Pressurised IntraPeritoneal Aerosolised Chemotherapy (PIPAC) in the management of cancers of the colon, ovary and stomach: a randomised controlled phase II trial of efficacy in peritoneal metastases.

Protocol

Vn5.0, 5th December 2024

Sponsor:	Cardiff and Vale University Health Board Joint Research Office, Lakeside Building 2nd Floor, University Hospital of Wales, Heath Park, Cardiff, CF14 4XW
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigators agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and Sponsor/CTR SOPs.

We agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

We also confirm that we will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Trial Sponsor:			
Name	**Position**	**Signature**	**Date**
Catherine Green	Research Governance Manager	Please see email dated 19.12.2024 for approval signature	19th December 2024
CTR Director:			
Name	**Signature**	**Date**	
Michael Robling	Please see email dated 19.12.2024 for approval signature	19th December 2024	
Chief Investigator:			
Names	**Signatures**	**Date**	
Sadie Jones	Please see email dated 20.12.2024 for approval signature	20th December 2024	
Jared Torkington	Please see email dated 20.12.2024 for approval signature	20th December 2024	

General Information This protocol describes the PICCOS clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

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TRIAL CO-ORDINATION

The PICCOS trial is being coordinated by the Centre for Trials Research (CTR) Cardiff University, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.
This protocol has been developed by the PICCOS Trial Management Group (TMG).
For **all queries** please contact the PICCOS team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigators

Main Trial Email:	**PICCOS@cardiff.ac.uk**
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Randomisation:

Randomisation
The randomisation system can be accessed via: https://redcap.ctr.cardiff.ac.uk/redcap/

Clinical queries:

Clinical queries
Please send any clinical queries to PICCOS@cardiff.ac.uk. All queries will be directed to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to the CTR Safety Team (ctr-safety@cardiff.ac.uk) within 24 hours of becoming aware of the event (See section 14 for more details).

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Glossary of abbreviations

5FU	Fluorouracil	**NIMP**	Non-Investigational Medicinal Product
AE	Adverse Event	**ORR**	Overall Response Rate
ALT	Alanine transaminase	**OS**	Overall Survival
AR	Adverse Reaction	**PAG**	Patient Advisory Group
AST	Aspartate transaminase	**PCI**	Peritoneal Cancer Index
C&C	Capability and Capacity	**PFS**	Progression free survival
C&V	Cardiff and Vale University Health Board	**PI**	Principal Investigator
CA125	Cancer Antigen 125	**PICCOS**	PIPAC In Cancers of the Colon, Ovaries and Stomach
CEA	Carcinoembryonic Antigen	**PIPAC**	Pressurised IntraPeritoneal Aerosolised Chemotherapy
CF	Consent Form	**PIS**	Participant Information Sheet
CI	Chief Investigator	**PM**	Peritoneal Metastasis
COS	Core Outcome Set	**POAC**	Pre-operative anaesthetic clinic
CPS	Combined Positive Score	**pPFS**	Peritoneal specific Progression Free Survival
CrCl	Creatinine Clearance	**PV**	Pharmacovigilance
CRF	Case Report Form	**QoL**	Quality of Life
CRS	Cytoreductive surgery	**R&D**	Research and Development
CT	Computerized Tomography	**RCT**	Randomised Controlled Trial
CTA	Clinical Trials Authorisation	**REC**	Research Ethics Committee
CTCAE	NCI Common Terminology Criteria for Adverse Events	**RECIST**	Response Evaluation Criteria in Solid Tumours
CTR	Centre for Trials Research	**RSI**	Reference Safety Information
DCR	Disease Control Rate	**SACT**	Systemic Anti-Cancer Therapy
DSUR	Development Safety Update Report	**SAE**	Serious Adverse Event
DPYD	Dihydropyrimidine dehydrogenase deficiency	**SAP**	Statistical Analysis Plan
ECG	Electrocardiogram	**SAR**	Serious Adverse Reaction
ECOG	Eastern Cooperative Oncology Group	**SmPC**	Summary Product Characteristics
EORTC	European Organisation for Research and Treatment of Cancer	**SoC**	Standard of Care
ePFS	Extraperitoneal Progression Free Survival	**SOP**	Standard Operating Procedure
ePIPAC	Electrostatic precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy	**SUSAR**	Suspected Unexpected Serious Adverse Reactions
EudraCT	European Clinical Trials Database	**TMF**	Trial Master File
FBC	Full Blood Count	**TMG**	Trial Management Group
FFPE	Formalin Fixed Paraffin Embedded	**TSC**	Trial Steering Committee
GCP	Good Clinical Practice	**TSF**	Trial Statistical File
GDPR	General Data Protection Regulations	**U&E**	Urea and Electrolytes
GMP	Good Manufacturing Practice	**UK**	United Kingdom
GP	General Practitioner	**IV**	Intravenous
HCRW	Health Care Research Wales	**kg**	Kilograms

HER2	Human epidermal growth factor receptor 2	**LFT**	Liver Function Test
HIPEC	Hyperthermic intraperitoneal chemotherapy	**LS**	Lesion Size
HR	Hazard Ratio	**MDT**	Multi-Disciplinary Team
HRA	Health Research Authority	**mg**	Milligrams
ID	Identifier	**MHRA**	Medicine and Healthcare products Regulatory Agency
IDEAL	Idea, Development, Exploration, Assessment, Long Term Study: Framework	**MMR**	Mismatch Repair
IDMC	Independent Data Monitoring Committee	**mOS**	Median Overall Survival
IMP	Investigational Medicinal Product	**MSI**	Micro-Satellite Instability
IP	Intraperitoneal	**NCA**	National Competent Authority
IRAS	Integrated Research Application System	**NHS**	National Health Service
ISF	Investigator Site File	**NICE**	National Institute for Health and Care Excellence
ISR	Investigator Safety Report	**NIHR**	National Institute for Health and Care Research
ISRCTN	International Standard Randomised Controlled Trial Number	**USM**	Urgent Safety Measure
IUS	Intrauterine hormone-releasing system	**WOCBP**	Women of Childbearing Potential
ISSPP	International Society for Study of Pleura and Peritoneum		

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
N/A	1.0		N/A
(N/A) Response to initial regulatory submission	2.0	13th September 2023	Section 9.3. Inclusion that a leaflet on risks of general anaesthetic from the Royal College of Anaesthetists will be given to patients in addition to trial PIS as part of consent process. Section 14.4. Correction to state that RSI can be found in section 4.8 of the relevant SmPC for IMPs used as per licensed indications. Removal of laparoscopic surgery RSI and RSIs for IP IMPs that were taken from the SmPCs for these IMPs (with intended IV routes of administration). RSI for PIPAC added. Section 14.8. Contraception advice updated in line with Clinical Trial Facilitation Group (CTFG) guidance on 'Recommendations related to contraception and pregnancy testing in clinical trials.'
SA01	3.0	19th September 2024	General changes: • Inconsistencies between sections corrected. • REC reference number added • ISRCTN added • Staffing change - Trial Administrator Changes relating to consent: • Section 9.3. Details added. 1 - patients can provide optional consent for collection of FFPE tumour blocks from initial diagnostic cancer biopsy/routine biopsies taken at PIPAC surgeries to be used for future ethically approved research. 2 - optional consent for these samples to undergo genetic analysis. 3 - optional consent for CT scan images relating to participant's disease

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
			(in addition to those performed in the trial) to be used for future ethically approved research. • Mention that Consent Logs need to be kept in ISF. Changes to eligibility criteria (Section 8): • Exclusion criteria for the ovarian group – removed '~~Radiological suspicion of involved lymph nodes (e.g. radiological features suspicious of malignancy).'~~ • Exclusion criteria for all groups – added 'Life expectancy <3 months' • Exclusion criteria for colorectal and stomach groups – added 'Previous CRS or HIPEC' Changes to trial objectives / outcomes (Section 5): • Changed wording of secondary outcomes ○ 'Incidence of CTCAE grade >3 ~~radiologically proven~~ bowel obstruction' ○ 'QoL (EORTC QLQ C30 + 3 other EORTC items)' • Added tertiary / exploratory objective 'To explore the effect of further anti-cancer treatment on overall survival ' • Added tertiary / exploratory outcome measure 'Details of anti-cancer treatment participants have had after trial treatment has ended' Changes to trial treatment: • Section 11.1. Removal of gemcitabine as a treatment option in the control arm of the ovarian group and as an IMP in the trial. • Section 11.1. Change to the dose permitted for liposomal doxorubicin in the ovarian group control arm from 50mg/m^2 to 40-50mg/m^2. • Section 11.1. Addition of 'intolerance' to the permitted reasons that a dose reduction of oxaliplatin IP/PIPAC is

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
			permitted from 120mg/m^2 to 90mg/m^2 in the colorectal group intervention arm. • Section 11.1. Removal of duration of administration for SACT drugs in all 3 disease treatment groups. • Section 11.3. Update to the preparation and storage details for prepared IP chemotherapy. • Section 11.3. Addition of text to state that patients with high BSA may not be able to receive full intended dose of 120mg/m^2 oxaliplatin. They can still have PIPAC, but a slightly lower dose may need to be given. • Section 11.4. Details on the administration of IP/PIPAC chemotherapy updated in accordance with the ISSPP training that PIPAC surgeons have received and in line with the PICCOS PIPAC Manual. • Section 11.13. Accountability requirements for IV and IP IMPs updated. • Section 11.15. Unused, prepared IP chemotherapy should be disposed of in theatre (according to local procedures) and not returned to pharmacy as previously mentioned. • Table 9 – "Clinical or radiological evidence of bowel obstruction" added as a contraindication for PIPAC. • Section 13. Addition of text "The operating theatre should be equipped with modern ventilation technology satisfying the HTM 03-01 Health Technical Memorandum Specialist Ventilation for Healthcare Premises." Laminar airflow is no longer a requirement for PIPAC • Section 13.1. Inclusion that PIPAC discharge information sheets are to be given to participants on discharge after each PIPAC procedure. Changes to trial assessments (Section 13):

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
			• Height only required to be measured and recorded on participant's first treatment cycle. • Inclusion that intervention arm participants must attend POAC prior to PIPAC 1. • Windows adjusted for when assessments are permitted to take place prior to and during each PIPAC treatment cycle. • Update on analysis time of CT scans of RECIST assessments. Changes relating to data management: • Section 17.2. Weblink for randomisation system updated to https://trials.cardiff.ac.uk/portal/. • Section 17.3, Update to text regarding quality of life questionnaires – these will now be entered into REDCap by site staff and no data entry will take place by CTR. Changes to sub-study (Section 6): • Removal of qualitative sub-study as this would have replicated the work of Taibi (2023) that identified 9 core outcomes for patients with peritoneal surface malignancies. 3 EORTC items added to the quality of life question set in PICCOS (this previously included EORTC QLQ-C30 only) to ensure that the full outcome set identified by Taibi 2023 is used in the trial.
SA02	4.0		Philip Markham has stepped down as Data Manager. Change to inclusion criteria for all disease groups (section 8.1): creatinine clearance reduced from ≥60ml to ≥50ml/min. Change to exploratory objectives (section 5.3): added "To explore stakeholder perspectives and experiences of PIPAC treatment, and PM disease more broadly, including their impact on symptoms and QoL. To determine the patient-

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
			related outcomes of interest for patients with PM, including those undergoing PIPAC treatment and SOC." Change to exploratory outcome measures: added "Patient-related outcomes of interest for patients with PM, including those undergoing PIPAC treatment and SOC, as determined by qualitative interviews with healthcare professionals and patients." Change to patient screening (section 9): inclusion that MMR test results are permitted for MSI testing. Addition of footnote to table 7 – assessments required prior to each SACT cycle "**Thyroid function tests and random blood glucose testing should be performed prior to each cycle for patients on Nivolumab as per local practice"* "Episodes of therapeutic ascitic drainage in ovarian cancer" added to tables 7, 8 and 10 to ensure this is recorded on the CRF at each treatment and follow up visit. Reinsertion of qualitative sub-study (section 5.3, 5.6, 6, 10.1, 19). The qualitative sub-study has been reinserted to explore QoL issues that are unique to patients with PM. This was initially taken out because a core outcome measure set for patients with PM was published during PICCOS development (Taibi et al. 2023). However, early observations during the first few months of opening the PICCOS trial have indicated potential deficiencies in the existing core outcome measure. The unique and broad patient cohort in the PICCOS trial with PM from three different tumour sites presents an excellent opportunity to enhance the existing core outcome measure set to be more representative of what's important for

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
			patients with PM from a variety of original tumour sites.
SA03			**Contact details section** • Change of Sponsor representative / Research Governance Manager from Maureen Edgar to Catherine Green. • Addition of Alys Humphrys as Trial Manager for the trial. • Change of CTR Director contact to from Richard Adams to Michael Robling **Section 8.1 Inclusion criteria** Inclusion criteria changed: • From 'Serum bilirubin ≤3 x ULN' to 'Serum bilirubin <30 micromol/L' • 'Creatinine clearance ≥50 mls/min. (*Creatinine clearance should be estimated using the online ClinCalc calculator: https://clincalc.com/kinetics/crcl.aspx*)' added **Section 10.1 Withdrawal** • Withdrawal Consent Form requires completion if participant withdraws from tumour samples being analysed and not other aspects of the trial as previously mentioned. **Section 11.1 Treatments. Table 4** • Weekly paclitaxel added as treatment regime for ovarian group control arm. • CAPOX-pembrolizumab and FOLFOX-pembrolizumab added as SACT option in stomach group • SACT options that include trastuzumab / nivolumab reformatted in table 4. An additional 1 day to the window that trastuzumab / nivolumab can be given

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			post PIPAC added with this update to facilitate scheduling. **Section 11.3 Treatment prescribing and dispensing (all disease groups)** • To assess PIPAC doses, the online ClinCalc calculator should now be used. Guidance removed that said ideal body weight should be used to calculate creatinine clearance in patients with high BMI. • Guidance added to state that local policy can be followed in how renal function is assessed in order to assess doses of SACT. **11.13 Accountability procedures** Addition of simple trial specific accountability log can be used for IV IMPs at sites that don't have aseptic dispensing worksheets. **11.14 Drug labelling** Pembrolizumab added to list of non IMPs **Table 9 - Requirements to be met prior to PIPAC** Do not give PIPAC unless 'CrCl in normal range' updated to 'Creatinine clearance ≥50 mls/min. (*Creatinine clearance should be estimated using the online ClinCalc calculator: https://clincalc.com/kinetics/crcl.aspx*)' **Section 13.3 Disease response assessment** Clarification and additional guidance added on site radiology and central radiology requirements. Site radiologists now not required to perform RECIST assessments of peritoneal disease. **Section 14.4 Expectedness** PIPAC RSI removed from the protocol and established as stand alone document.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
			Section 17.2 Completion of CRFs Link to randomise a patient updated to https://redcap.ctr.cardiff.ac.uk/redcap/

2. Synopsis

Short title	Pressurised IntraPeritoneal Aerosolised Chemotherapy (PIPAC) in the management of cancers of the colon, ovary and stomach: a randomised controlled phase II trial of efficacy in peritoneal metastases.
Acronym	PICCOS
Sponsor ref. no.	21/SEP/8237E
Clinical phase	Phase II
Funder and ref.	NIHR EME: NIHR151274
Trial design	Multicentre, unblinded, phase II, basket trial, randomised controlled trial
Trial participants	Patients with colorectal, ovarian or stomach cancer with peritoneal metastases (PM)
Planned sample size	Colorectal group: 78 Ovarian group: 66 Stomach group: 72
Planned number of sites	10 PIPAC sites and 30 Recruiting sites
Inclusion criteria	**All disease groups:** 1) 16 Years and older. 2) Visible (measurable or non-measurable) peritoneal lesion(s) on computerised tomography (CT) imaging as per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. 3) Eastern Cooperative Oncology Group (ECOG) performance status 0–1 4) Adequate bone marrow, liver and kidney function (within 7 days prior to randomisation): a) Neutrophil ≥ 1.5×10^9/L b) White blood cells ≥ 3.0×10^9/L c) Platelets ≥ 100×10^9/L d) Haemoglobin ≥ 90 g/l e) Serum bilirubin <30 micromol/L *f)* ALT/AST ≤ 2.5 x ULN *(if both done, both must meet criteria)* g) Creatinine clearance ≥50 mls/min. (*Creatinine clearance should be estimated using the online ClinCalc calculator: https://clincalc.com/kinetics/crcl.aspx*) 5) Fit enough to receive full dose of systemic anti-cancer therapy (SACT) in cycle 1 as defined in the protocol. 6) Ability to provide informed consent obtained prior to any trial-specific screening procedures. **Colorectal group only:** 7) PM from histologically proven primary adenocarcinoma of the colorectum. **Ovarian group only:** 8) PM from histologically confirmed primary epithelial ovarian, tubal, or primary peritoneal platinum-resistant carcinoma (including clinical

	recurrence, refractory disease, or persistent disease within 6 months of last chemotherapy). **Stomach group only:** 9) PM from histologically proven primary adenocarcinoma (any subtype) of stomach or Siewert type 3 gastro-oesophageal junction tumour (any Human Epidermal Growth Factor Receptor 2 (HER2) status or Combined Positive Score (CPS)).
Exclusion criteria	**All disease groups:** 1) Any prior malignancy not considered in complete remission for at least 2 years, excluding non-melanoma skin cancer. 2) Pregnant or breastfeeding. 3) Untreated central nervous system disease or symptomatic central nervous system metastasis, history or evidence of thrombotic or haemorrhagic disorders not considered currently in complete remission. 4) Bevacizumab / Aflibercept should not be used in either arm (minimum 4 weeks from any prior Bevacizumab / Aflibercept). 5) Contraindication to any drug contained in the chemotherapy regimen. 6) Medical, geographical, sociological, psychological, or legal conditions that would prevent the patient from completing the study or signing the informed consent. 7) Unresolved bowel obstruction or parenteral nutrition or gastric tube. 8) Contraindication to surgery. 9) Participating in other oncological trials that may impact on endpoint. 10) Life expectancy <3 months **Colorectal group only:** 1) Extra-peritoneal metastases except for: a. retroperitoneal lymph nodes <2cm b. lung metastases; with < 5 lung metastases none >1cm 2) Eligible for and choses cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) upfront. 3) Prior systemic therapy for colorectal cancer in the last 6 months. 4) Dihydropyrimidine Dehydrogenase Deficiency (DPYD) variant detected. 5) Microsatellite instability (MSI) high. 6) Previous cytoreductive surgery (CRS) or Hyperthermic Intraperitoneal Chemotherapy (HIPEC). **Ovarian group only:** 1) Extra-peritoneal metastases (with the exception of retroperitoneal lymph nodes). 2) Parenchymal liver or spleen metastases. 3) Malignant pleural effusion. 4) Non-epithelial pathology subtype. 5) Peritoneal disease, amenable to surgical resection. **Stomach group only:**

	1) Extra-peritoneal metastases (with the exception of retroperitoneal lymph nodes). 2) Prior SACT, radiotherapy or surgery for stomach cancer. 3) Gastric or duodenal stent in-situ. 4) Gastro-oesophageal junction Siewert Type 1 or Type 2 tumour. 5) Symptoms and/or radiology suggestive of impending and/or current bowel obstruction. 6) Uncontrolled and persistent ascites. 7) MSI high. 8) DPYD variant detected. 9) Previous CRS or HIPEC.		
Treatment duration	Colorectal group	Intervention arm	18 weeks
		Control arm	18 weeks
	Ovarian group	Intervention arm	14-15 weeks
		Control arm	24 weeks
	Stomach group	Intervention arm	18 or 21 weeks
		Control arm	18 weeks
Follow-up duration	Participants will be followed up for a minimum 6 months from their date of randomisation		
Planned trial period	• Trial set up: 6 months. Recruitment period: 2.5 years. Follow up period: at least 6 months from randomisation. Analysis and report writing: 6 months. 4 years total.		
Primary objective	• To determine if PIPAC given with (colorectal, stomach) or instead of (ovarian) SACT improves Peritoneal Progression Free Survival (pPFS) compared to standard SACT.		
Secondary objectives	• To determine how PIPAC impacts quality of life (QoL) compared to standard of care (SOC). • To determine the safety of PIPAC in terms of the proportion of patients experiencing toxicity and/or surgical complications, compared with SACT only group. • To determine the proportion of patients who complete three PIPAC procedures. • To determine if disease can be reduced to the point of resectability. • To evaluate Overall Survival (OS) in both groups. • To evaluate overall Progression Free Survival (PFS) in both groups. • To assess the impact on patient's symptoms (and need for intervention to relieve them – in ovarian cancer). • To determine peritoneal specific overall response rate (ORR) and disease control rate (DCR).		
Tertiary/Exploratory objectives	• To determine the feasibility of randomisation.		

	• To evaluate and compare between the two arms the response of Carcinoembryonic Antigen (CEA) (in colorectal cancer) and Cancer Antigen 125 (CA125) (in ovarian cancer) with the radiological response of peritoneal disease. • To cross correlate the radiological evaluation to assess scan effectiveness and mismatches with PCI scoring at laparoscopy. • To explore the effect of further anti-cancer treatment on overall survival. • To explore stakeholder perspectives and experiences of PIPAC treatment, and PM disease more broadly, including their impact on symptoms and QoL. • To determine the patient-related outcomes of interest for patients with PM, including those undergoing PIPAC treatment and SOC.
Primary outcomes	• pPFS

Secondary outcomes	• QoL (EORTC QLQ C30 + 3 other EORTC items)
	• Safety and surgical complication rates
	  ○ Toxicity and grade according to NCI Common Terminology Criteria for Adverse Events (CTCAE) V5.0
	  ▪ Episodes of neutropenic sepsis
	  ○ Clavien Dindo classification (within 30 days of each PIPAC)
	  ○ Incidence of CTCAE grade ≥3 bowel obstruction
	• Proportion of patients completing 3 PIPAC procedures, and reasons why not if <3 completed.
	• Number of conversions to operable disease in stomach or colorectal cancer
	• OS, defined as days from randomisation to death for any reason.
	• PFS. This is defined as the time from date of randomisation to the date of progression (anywhere in the patient) or death from any cause.
	  ○ Extraperitoneal Progression free survival (ePFS), defined as the time from date of randomisation to the date of progression (outside of the peritoneum) or death from any cause.
	• Episodes of therapeutic ascitic drainages (in ovarian cancer)
	• Peritoneal specific ORR observed at any time during treatment and follow-up.
	• Peritoneal specific DCR defined as the proportion of patients with complete response, partial response or stable disease maintained at end of treatment scan (i.e. 3rd scan).

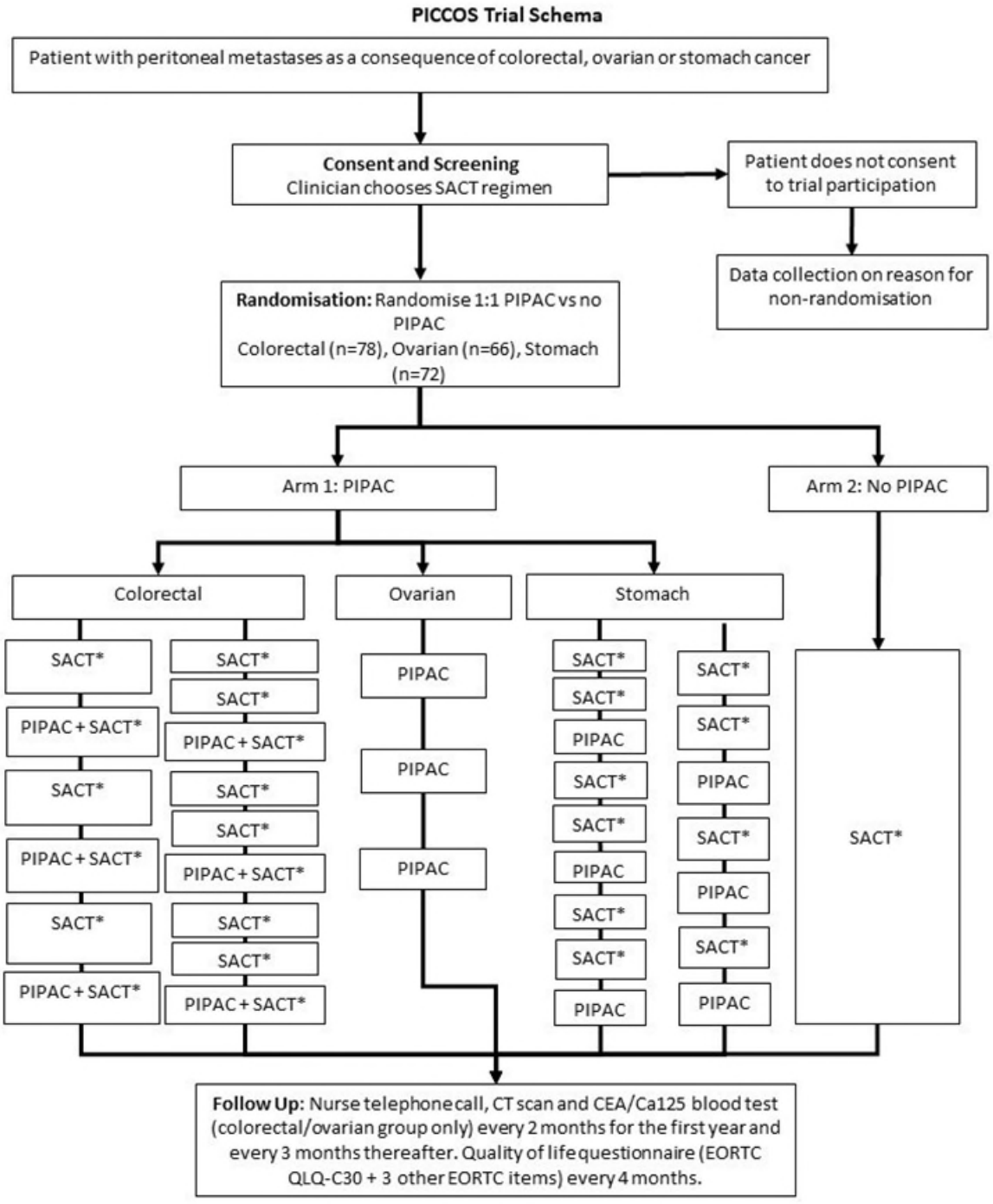
Tertiary/Exploratory outcomes	• The proportion of eligible patients who consent to randomisation out of those invited to take part.

	• CEA (in colorectal cancer) and CA125 (in ovarian cancer) response from baseline to the end of follow up. • PCI scoring at laparoscopy. • Details of anti-cancer treatment participants have had after trial treatment has ended • Patient-related outcomes of interest for patients with PM, including those undergoing PIPAC treatment and SOC, as determined by qualitative interviews with healthcare professionals and patients.
Investigational medicinal products (IMPs)	For Colorectal group: • Oxaliplatin 120mg/m^2 IP as PIPAC (dose reduction to 90mg/m^2 for patients with frailty, intolerance or neuropathy as agreed by site oncologist). • Mitomycin 7.5mg/m^2 IP as PIPAC for patients who are hypersensitive to, or unable to have oxaliplatin.
	For Ovarian group: • Cisplatin 10.5mg/m^2 IP as PIPAC • Doxorubicin 2.1mg/m^2 IP as PIPAC • Paclitaxel 80mg/m^2 IV • Liposomal doxorubicin 40-50mg/m^2 IV
	For Stomach group: • Cisplatin 10.5mg/m^2 IP as PIPAC • Doxorubicin 2.1mg/m^2 IP as PIPAC

3 Trial summary & schema

3.1 Trial schema/ Participant flow diagram

Figure 1: Trial Schema



* SACT = Systemic Anti-Cancer Therapy. Should be as per standard of care options listed within the PICCOS protocol. There are 2 or 3 weekly options for colorectal/ stomach groups, regimen given is chosen by treating clinician, ovarian SACT is 4 weekly.

3.2 Trial lay summary

Aims

Bowel, ovarian and stomach cancer will often spread (metastasise) to the lining (peritoneum) of the abdominal cavity. This trial aims to determine if a new way of delivering chemotherapy as a spray, directly into the peritoneal cavity, would improve survival in patients with peritoneal metastases, compared to conventional intravenous chemotherapy. Critically, we will also assess the impact of treatment on patient QoL.

Background

Up to 13%, 50% and 14% of patients with bowel, ovarian and stomach cancer respectively, present with peritoneal metastases. When this form of spread occurs, patients are normally informed that their disease is incurable. As well as a relatively rapid decline, peritoneal metastases can cause a series of unpleasant symptoms due to new tumour growth. Peritoneal metastases are difficult to treat with conventional anticancer drugs and there is an urgent need to develop new treatment strategies. A new strategy showing potential is Pressurised IntraPeritoneal Aerosol Chemotherapy (PIPAC). PIPAC delivers anti-cancer drugs into the peritoneal cavity as an aerosol during keyhole surgery. PIPAC has been shown to deliver higher doses of chemotherapy directly to tumour sites compared to conventional treatment, with fewer side-effects due to less chemotherapy circulating in the blood. PIPAC has been shown to be both safe and feasible in a series of clinical trials. The question that now remains is whether PIPAC is effective or not. The National Institute for Health and Care Excellence (NICE) has recommended that PIPAC should only be offered to United Kingdom (UK) patients within a research trial setting. There are trials for patients in Europe but not in the UK.

Design and Methods

This randomised controlled trial will be open to patients with bowel, ovarian or stomach cancer. Each cancer type will have individual eligibility criteria and protocols to allow for the necessary variations in treatment. In all cancer types, patients will be randomised to receive either standard chemotherapy delivered via the bloodstream or a combination of standard chemotherapy and/or PIPAC, where three PIPAC procedures are performed. This trial design enables the variation required to include patients with different cancer types and the ability to stop the trial for any one cancer type if it is not working whilst continuing with the others.

Patient and Public involvement

Many patients in the UK are aware of PIPAC treatment with specialists frequently approached by patients and carers requesting it. This has been a driving force in developing this trial. Patients have been involved from an early stage and helped to determine acceptable time points for investigations, design travel policies, select the best QoL assessment tools, define the priority of research questions and write the proposal to this point. They will continue to support trial design, raise trial awareness and ensure patient concerns and well-being are given paramount importance going forwards. PIPAC has excited much interest in patient groups. We will disseminate trial results through social media, relevant charitable organisations, presentation at academic conferences, peer-reviewed journals, and through the Centre for Trials Research (CTR) trial web page. Information leaflets, public presentations and media coverage are integral elements of our public engagement plans. The results will strongly influence future NICE review of PIPAC use in the UK.

4 Background

Colorectal, ovarian and stomach cancers account for 24,500 deaths a year in the UK. When these tumours spread or recur within the peritoneum, they are generally deemed incurable as no effective treatment strategy exists (1–3). As many as 10% of colorectal, 50% of ovarian and 14% of stomach cancers will have PM at the time of presentation (4). In colorectal cancer, 2% have peritoneal disease as the only site of metastases. A minority of fit patients with low volume disease may be suitable for major surgery in combination with Hyperthermic Intraperitoneal Chemotherapy (HIPEC). However, for many this is not an option as it is not suitable for extensive disease and patients must have a high level of fitness to tolerate such an invasive procedure. Patients unable to undergo or access HIPEC have a median PFS of 6 months and OS of 16.3 months (5). In ovarian cancer 25% of patients will have disease that is resistant to platinum chemotherapy. Platinum resistance is a poor prognostic factor with a median PFS of 3-4 months and OS of 9-13 months (6–8). Patients with stomach cancer and PM have a particularly poor OS of 3-6 months, extended to 9-11 months with standard SACT (9,10). PM can cause ascites and bowel obstruction leading to abdominal pain, nausea, vomiting and significant suffering. Patients are left with an uncertain future, reduced QoL and very few treatment options. It is clear and is acknowledged by the clinical community that standard SACT across all three disease groups is not having the desired impact. Peritoneal metastatic disease represents a significant unmet clinical need and there is an urgent need for improved treatments for these poor prognosis patient groups. A novel anti-cancer technology is PIPAC. PIPAC aims to improve target specificity of anti-cancer therapies such as chemotherapy by delivering the medication directly to the PM (11,12). Chemotherapy is delivered as an aerosol into the closed abdominal cavity at conventional laparoscopy. It is suggested that the small size of the droplets under the raised intraperitoneal pressure utilised during laparoscopy drives the chemotherapy directly into the tumour nodules. There is reduced systemic absorption creating a greater local tumour effect and reducing the common side effects of systemic chemotherapy.

The PICCOS trial (PIPAC In Cancers of the Colon, Ovaries and Stomach) is a multi-arm, prospective, randomised controlled trial (RCT) designed to provide high quality evidence regarding the efficacy of PIPAC in improving PFS. PIPAC has already achieved rapid uptake across Europe, driven often by patient demand and clinician enthusiasm. However, high quality efficacy data is lacking and is required now. In October 2021, NICE Interventional Procedures Guidance (IPG681) for PIPAC was published and stipulated that PIPAC should only be used within the context of research. The NICE stated that this research should be in the form of RCTs to demonstrate efficacy compared to standard treatments (13). PICCOS will provide the opportunity to address this in the UK and provide direction for future phase III trials. PICCOS will provide a unique opportunity to further understand impact of PIPAC on patients with PM on patient QoL.

Our team initially approached NICE and provided evidence highlighting PIPAC as a subject of interest. The NICE statement document (IPG681) was published, concluding that the existing evidence signalled that PIPAC may improve disease response, PFS, OS and QoL, but the research was heterogeneous in quality and described infrequent but serious side effects (13). NICE were clear in recommending that in the UK, PIPAC should only be performed in the context of an RCT. Without establishing such a trial, we will be unable to address the existing knowledge gap. Prior to the NICE statement we had established the UK PIPAC collaborative to investigate PIPAC as a treatment modality. In response to the NICE statement the PICCOS trial developed. We are aware of no additional ongoing or planned RCTs assessing PIPAC in the UK currently.

We initially conducted comprehensive literature reviews to fully understand the existing evidence base and inform the design of the PICCOS trial. In 2020, we published a review of the worldwide introduction of PIPAC in relation to the Idea, Development, Exploration, Assessment, Long-Term

(IDEAL) Study framework. This review identified 86 relevant publications but no RCTs and concluded that there was acceptable safety data, but a lack of robust prospective data on the efficacy of the treatment (14) and was updated and republished in 2022 (16). Our updated review has demonstrated that many of the registered studies and published evidence worldwide remain in the early phases of the IDEAL framework underlining the need for high quality clinical trials. We have also undertaken a systematic review of the literature specifically relevant to stomach cancer that was published in October 2022 (15) and are currently undertaking the same for ovarian cancer. Both are registered on the PROSPERO database (16,17). A systematic review for colorectal cancers was published in 2021 by another group so this has not been repeated (18). The searches for these studies were conducted on Medline and Ovid databases using search terms to include studies involving PIPAC and peritoneal metastases, irrespective of cancer origin, up to 28th February 2022. ClinicalTrials.gov and the EU Clinical Trials registers were searched for trial registrations (up to 19th January 2022) involving PIPAC. The list illustrates the impact of the NICE statement and the importance of establishing a UK based RCT. The teams from Lyon and Paris have already indicated their interest in future pooling of appropriate RCT data for meta-analysis with us.

This approach of strong scientific exploration through RCT data and international collaboration will lead to the most rapid understanding of the efficacy of PIPAC and its effect on patient QoL. The adoption and optimisation of PIPAC (or indeed its discard) as a treatment modality will lead to a step change in patient care across the world.

4.1 Laboratory studies

The published laboratory studies include the use of simulators, animal models, cell lines, in vitro and ex vivo studies. The first description of a "therapeutic pneumoperitoneum", was using an in vivo swine model, published in 2000(19). Studies demonstrated superiority of PIPAC over conventional lavage with regards to peritoneal distribution and depth of drug penetration using methylene blue dye, and Dbait (non-coding DNA fragments) with a fluorescent marker (20,21). Further studies, utilising both in vivo and ex vivo swine models and a laparoscopic box simulator, demonstrated that depth of drug penetration was highest closest to the delivery device, and that distribution of the aerosol around the peritoneum was heterogeneous (22–24). Parameters to optimise drug penetration and distribution were explored; in one study, increasing the intra-abdominal pressure to 15mmHg (from 12mmHg) increased the cytotoxic action of oxaliplatin on an in vitro human colon adenocarcinoma cell line, but a higher temperature did not have a significant effect (25).

4.2 Experimental medicine studies

Attempts have been made to optimise the technique in vitro. These include demonstrating the stability of nano or micro particles (26,27), the successful use of an anti-adhesive polymer as a delivery system (28) demonstrating that liposomal doxorubicin caused almost complete inhibition of drug action during PIPAC (29). Further experiments aimed to address the issue of non-homogenous drug distribution with the use of a rotational or multi-directional nozzle, to change the direction of spray in the abdomen (30,31). Use of these devices with in vivo swine models demonstrated wider distribution than the conventional microinjection pump. A modification involved the use of electrostatic precipitation and was named ePIPAC (32). Improvement of spatial distribution and tissue penetration was shown with the addition of an electrostatic charge (ePIPAC) to fluorescent albumin bound paclitaxel nanoparticles in a rat model (33).

4.3 Pilot data

The first in-human studies were performed by the Bochum group on patients with PM and no alternative treatment options and published in 2013 and 2014 (34,35). They demonstrated histological

tumour regression of peritoneal disease in the three patients treated, with limited renal and liver toxicity despite repeated PIPAC cycles. The surgical set-up described would become the most widely used technique, and consisted of pressurised aerosolization of cisplatin and doxorubicin, with a CO_2 pneumoperitoneum at a pressure of 12 mmHg over 30 mins, at a temperature of 37°C. Dosage of cisplatin (7.5mg/m^2 body surface) and doxorubicin (1.5mg/m^2 body surface) were set as 10% of their usual systemic dose.

Occupational health studies demonstrated safety for theatre staff (36), although almost all new groups embarking on PIPAC each performed their own occupational safety tests despite using similar equipment and operating procedures (37–39).

4.4 Epidemiological or case series data

Case reports were used to describe the first use of PIPAC for different indications, including pancreatic cancer, PM in organ donor recipients, ovarian cancer and pseudomyxoma peritonei (40–42). Complications included peritoneal sclerosis and rare instances of severe hypersensitivity reactions to platinum (43,44). The latter was described in a case series involving 132 patients, of whom four (3%) had a severe reaction to platinum, manifesting instantaneously, to 50 minutes after application of PIPAC.

4.5 Initial cases series

One study assessed QoL in 91 patients at admission and after their first and second round of PIPAC treatment. A moderate transient increase in pain score was found, but no therapy related decrease in the QoL score was demonstrated (45). The most commonly used chemotherapy regimen used in PIPAC is either oxaliplatin as a sole agent or cisplatin with doxorubicin. Over the last few years, progress has been made regarding formal dose escalation studies. In a phase I study, the Bochum group found that patients undergoing PIPAC could tolerate an increase in the dose of cisplatin and doxorubicin to 10.5mg/m^2 and 2.1mg/m^2 respectively (46). A French group found that the maximum tolerated dose of oxaliplatin was 90 mg/m^2 (47), due to dose-limiting toxicity at the higher dose of 140mg/m^2 (grade IV allergic reaction and grade III neutropenia). However, the Turin group found in their phase 1 dose escalation study that patients (n=3) could tolerate a maximum dose of 135 mg/m^2 (48) with no dose-limiting toxicity observed. They also looked at cisplatin and doxorubicin and found a maximum dose of 30mg/m^2 and 6mg/m^2; significantly higher than used in any previous PIPAC application. Common adverse events across all these studies included nausea, vomiting and abdominal pain.

Colorectal

There are no published RCTs of PIPAC in patients with colorectal cancer. PIPAC has an acceptable safety profile and is feasible in patients with colorectal PM with oxaliplatin being the commonest agent used (18). Median OS with the use of PIPAC in non-randomised studies ranges from 8-27 months but with variability in treatment regimens, especially in the stratification between those receiving prior systemic therapy (49–53).

Ovarian

There are no published RCTs of PIPAC in patients with ovarian cancer, studies are either single-arm prospective or retrospective. There are four retrospective studies and one prospective study reporting median overall survival ranging from 6.8–22 months (52–56). The study populations amongst these trials were heterogeneous varying from primary presentation patients to platinum resistant recurrent cases. In 2015, Tempfer et al performed a prospective cohort study assessing mean PFS in 64 patients with recurrent ovarian cancer (platinum resistant and sensitive) and reported PFS of 144 days and 174 days and overall, 1-year survival of 50% and 63% in the intention to treat and per-protocol subgroups

respectively (56). A prospective study of 21 patients with unresectable peritoneal metastasis undergoing PIPAC with systemic chemotherapy compared patients who had received bevacizumab with those who had not (57).

Stomach

There are no published RCTs of PIPAC in stomach cancer to determine efficacy, the studies are either single arm prospective or retrospective. There have been 11 retrospective (52,54,58–66) and four prospective studies (50,51,67,68). Median overall survival (mOS) ranged from 8 – 19.1 months and 1-year OS between 49.8-77.9%. Reporting of histological response was heterogeneous, but complete response was reported in 0-35%, and partial response in 0-83.3%. Grade 3 and 4 toxicity was 0.7-25% and 0-4.1% respectively. Three studies assessed QoL, reporting no significant difference after PIPAC (50,58,68). A published systematic review with an emphasis on patients with ovarian cancer but including patients with colorectal and stomach cancer too, investigated the safety and efficacy of PIPAC demonstrated proof of concept within 28 clinical trials including 1547 patients (69). No RCTs were identified. It concluded that PIPAC was technically feasible in 89% of cases. Safety analysis of 1197 cases revealed adverse events CTCAE grades 4 and 5 in 10 (0.8%) and 19 (1.6%) of patients respectively. Pooled analysis revealed an overall tumour regression rate of 69% (184/264) and an improvement of peritoneal cancer index (PCI), in 69% (116/168). Further analysis of three studies reported a mean PFS of 5.8 months and in 17 studies an OS of 13.7 months. QoL was maintained in all studies with improvement of global health reported in four studies.

5 Trial objectives/endpoints and outcome measures

5.1 Primary objectives

- To determine if PIPAC given with (colorectal, stomach) or instead of (ovarian) SACT improves pPFS compared to standard SACT.

5.2 Secondary objectives

- To determine how PIPAC impacts QoL compared to SOC.
- To determine the safety of PIPAC in terms of the proportion of patients experiencing toxicity and/or surgical complications, compared to the SACT only group.
- To determine the proportion of patients who complete three PIPAC procedures.
- To determine if disease can be reduced to the point of resectability.
- To evaluate OS in both groups.
- To evaluate overall PFS in both groups.
- To assess the impact on patient's symptoms (and need for intervention to relieve them – in ovarian cancer).
- To determine peritoneal specific ORR and DCR.

5.3 Tertiary/Exploratory objectives

- To determine the feasibility of randomisation
- To evaluate and compare between the two arms the response of CEA (in colorectal cancer) and CA125 (in ovarian cancer) with the radiological response of peritoneal disease.

- To cross correlate the radiological evaluation to assess scan effectiveness and mismatches with PCI scoring at laparoscopy.
- To explore the effect of further anti-cancer treatment on OS.
- To explore stakeholder perspectives and experiences of PIPAC treatment, and PM disease more broadly, including their impact on symptoms and QoL.
- To determine the patient-related outcomes of interest for patients with PM, including those undergoing PIPAC treatment and SOC.

5.4 Primary outcome measure

- pPFS - defined as the interval between the date of randomisation and the first radiologically documented progression of peritoneal disease or the date of death from any cause. The pPFS interval measurement will be regardless of intercurrent events of SACT or PIPAC discontinuation, or any change to treatment. Peritoneal disease progression will be assessed using RECIST V1.1 criteria based on CT scans performed according to disease group schedules.

5.5 Secondary outcome measures

- QoL (EORTC QLQ C30 + 3 other EORTC items)
- Safety and surgical complication rates
    - Toxicity and grade according to NCI CTCAE V5.0
        - Episodes of neutropenic sepsis
    - Clavien Dindo classification (within 30 days of each PIPAC)
    - Incidence of CTCAE grade $\geq$3 bowel obstruction
- Proportion of patients completing three PIPAC procedures, and reasons why not if <3 completed.
- Number of conversions to operable disease in stomach or colorectal cancer.
- OS, defined as days from randomisation to death for any reason.
- PFS. This is defined as the time from date of randomisation to the date of progression (anywhere in the patient) or death from any cause.
    - ePFS, defined as the time from date of randomisation to the date of progression (outside of the peritoneum) or death from any cause.
- Episodes of therapeutic ascitic drainages (in ovarian cancer).
- Peritoneal specific ORR observed at any time during treatment and follow-up.
- Peritoneal specific DCR defined as the proportion of patients with complete response, partial response or stable disease maintained at end of treatment scan (i.e. 3rd scan).

5.6 Tertiary/Exploratory outcomes

- The proportion of eligible patients who consent to randomisation out of those invited to take part.
- CEA (in colorectal cancer) and CA125 (in ovarian cancer) response from baseline to the end of follow up.

- PCI scoring at laparoscopy.
- Details of anti-cancer treatment participants have had after trial treatment has ended
- Patient-related outcomes of interest for patients with PM, including those undergoing PIPAC treatment and SOC, as determined by qualitative interviews with healthcare professionals and patients.

6 Trial design and setting

This is a Phase II, unblinded, multicentre, superiority basket randomised controlled trial. Patients will be identified through clinicians at Multi-Disciplinary Team (MDT) meetings in selected recruiting centres. Recruiting clinicians will log onto a central web-based platform that will randomise patients in a 1:1 ratio to either standard of care SACT or the PIPAC intervention arm. We aim to recruit 78 colorectal, 66 ovarian and 72 stomach cancer patients over 2.5 years, and follow-up will last a minimum of 6 months for all participants.

Allocation will be minimised by PIPAC centre to ensure there is not a disparity in per patient resource costs between PIPAC sites and balanced on prognostic factors for each cancer type to avoid bias. Within each centre and disease site, the first patient will be allocated at random, and then minimisation with a 20% random element will be used to allocate the next patient to the treatment which reduces the overall imbalance across all prognostic factors.

The PICCOS trial had originally intended to explore QoL issues that are unique to patients with peritoneal metastases undergoing PIPAC and identify / develop a patient reported outcome scale or item which captured the specific QoL issues faced by patients. A core set of patient-reported outcomes for peritoneal surface malignancies was published in August 2023 (70). The core outcome set (COS) was developed using a two-round Delphi process involving healthcare professionals, patients and researchers across five centres in France and Switzerland, in line with published recommendations for COS development. Nine core outcomes were identified: (i) General QOL; (ii) General Health; (iii) Physical ability; (iv) Physical fatigue; (v) Ability to work or perform usual activities; (vi) Anxiety; (vii) Fear of recurrence; (viii) Abdominal pain, and (ix) Satisfaction with the medical team. All nine of the core outcomes are measured in existing validated tools developed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group. The majority (six of the nine outcomes) are captured in the EORTC QLQ-C30 (a 30-item 'core' questionnaire designed to assess health-related quality of life (HRQL) in any cancer population/disease site) as either multi-item scales or as single items. In view of this, the planned qualitative sub-study is no longer needed. The EORTC QLQ-C30 is already being used in PICCOS. With Substantial Amendment 01, three additional items (fear of recurrence, abdominal pain and satisfaction with the medical team) have been added to the QoL question set that will be given to trial participants within the PICCOs trial.

Within this trial, there is a sub-study that will explore QoL issues that are unique to patients with PM.

The PICCOS trial will also collaborate as a 'host' trial with the Medical Research Council (MRC) funded PrinciPIL study: Developing Core Principles for Sharing Information about Potential Intervention Benefits and Harms in Patient Information Leaflets (Research Ethics Committee (REC) reference 22/PR/0063, IRAS 305945) to embed the PrinciPIL 'Study Within a Trial' (SWAT) sub-study.

6.1 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/ Department of Health (DH)/ Medicines and Healthcare Regulatory Agency (MHRA) Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects.
- How high the risk is compared to normal standard practice.
- How the risk will be minimised/managed.

This trial has been categorised as a TYPE B, where the level of risk is somewhat higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager (TM). The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 25.1).

7 Site and Investigator selection

This trial will be carried out at participating National Health Service (NHS) sites within the UK. All sites who are interested in participating will be required to complete a registration form to confirm that they have adequate resources and experience.

Up to 40 sites will be opened in total. All sites will be able to recruit and deliver SACT. It is anticipated that 10 sites, geographically spread across the UK, will deliver PIPAC treatment (PIPAC Sites). The remaining sites will be required to refer patients to PIPAC sites when randomised for PIPAC treatment.

In all sites there will be one named Principal Investigator (PI) for the purposes of the IRAS and overall responsibility, and it will be a local decision as to whether this will be an oncologist or surgeon. Each site will have up to 7 Co-PIs (surgery/oncology for each cancer site and single radiologist) depending on local requirements and preference.

The following documents must be in place and copies sent to PICCOS@cardiff.ac.uk before site initiation.

- Confirmation of Capacity and Capability (C&C) from Research and Development (R&D) department following sharing of local information pack.
- A signed Trial Agreement.
- Current Curriculum Vitae and Good Clinical Practice (GCP) training certificate of the PI.
- Completed Site Delegation Log.
- Full contact details for all host care organisation personnel involved, indicating preferred contact.
- A copy of the most recent approved version of the trial Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper.
- A copy of the most recent approved versions of the PICCOS PIPAC discharge information sheet(s) on host care organisation headed paper – applicable to PIPAC sites only.

- A copy of the most recent approved General Practitioner (GP) letters on host care organisation headed paper.
- A copy of the Withdrawal Consent Form on host care organisation headed paper.
- A set of laboratory normal ranges and laboratory certification/accreditation from the host care organisation laboratory being used for analyses.
- Copy of the certificates from at least two surgeons at site confirming completion of the International Society for Study of Pleura and Peritoneum (ISSPP) course on PIPAC (or equivalent) – applicable to Type B/PIPAC sites only.

The following will be obtained and provided to site by the PICCOS trial team:

- Favourable opinion of host care organisation/PI from Research Ethics Committee (REC).
- Favourable opinion of Health Research Authority/ Health Care Research Wales (HRA/HCRW).
- MHRA approval.
- Site File (including guidance documentation, SAE forms, PIPAC Manual etc).
- Pharmacy Site File (Including Pharmacy Manual).

Upon completion of all the above documents, the CTR TM will send written confirmation to the PI/lead Research Nurse detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive their trial equipment and a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. The CTR will issue the site with the latest version of the documents as soon as they have the necessary approvals and become available. It is the responsibility of the CTR to ensure that they obtain confirmation of continued C&C for the new documents.

Site initiation will be conducted either in person or via video conferencing.

8 Participant selection

Participants are eligible for the trial if they meet all of the relevant following inclusion criteria for their disease group and none of the exclusion criteria for their disease group apply. All queries about participant eligibility should be directed to the CTR TM before randomisation. Eligibility waivers will not be permitted.

8.1 Inclusion criteria

All disease groups:

1) 16 Years and older
2) Visible (measurable or non-measurable) peritoneal lesion(s) on CT imaging as per RECIST v1.1
3) ECOG performance status 0–1
4) Adequate bone marrow, liver and kidney function (within 7 days prior to randomisation):
   a) Neutrophil ≥ 1.5×10^9/L
   b) White blood cells ≥ 3.0×10^9/L
   c) Platelets ≥ 100×10^9/L

d) Haemoglobin ≥ 90 g/l
e) Serum bilirubin <30 micromol/L
f) ALT/AST ≤ 2.5 x ULN (*(if both done, both must meet criteria)*
g) Creatinine clearance ≥50 mls/min. (*Creatinine clearance should be estimated using the online ClinCalc calculator: https://clincalc.com/kinetics/crcl.aspx*)

5) Fit enough to receive full dose of SACT in cycle 1 as defined in the protocol.
6) Ability to provide informed consent obtained prior to any trial-specific screening procedures.

Colorectal group only:

1) PM from histologically proven primary adenocarcinoma of the colorectum

Ovarian group only:

1) PM from histologically confirmed primary epithelial ovarian, tubal, or primary peritoneal platinum-resistant carcinoma (including clinical recurrence, refractory disease, or persistent disease within 6 months of last chemotherapy).

Stomach group only:

1) PM from histologically proven primary adenocarcinoma (any subtype) of stomach or Siewert type 3 gastro-oesophageal junction tumour (any HER2 status or CPS).

8.2 Exclusion criteria

All disease groups:

1) Any prior malignancy not considered in complete remission for at least 2 years, excluding non-melanoma skin cancer.
2) Pregnant or breastfeeding.
3) Untreated central nervous system disease or symptomatic central nervous system metastasis, history or evidence of thrombotic or haemorrhagic disorders not considered currently in complete remission.
4) Bevacizumab / Aflibercept should not be used in either arm (minimum 4 weeks from any prior Bevacizumab / Aflibercept).
5) Contraindication to any drug contained in the chemotherapy regimen.
6) Medical, geographical, sociological, psychological or legal conditions that would prevent the patient from completing the trial or signing the informed consent.
7) Unresolved bowel obstruction or parenteral nutrition or gastric tube.
8) Contraindication to surgery.
9) Participating in other oncological trials that may impact on endpoint.
10) Life expectancy <3 months.

Colorectal group only:

1) Extra-peritoneal metastases except for:
   a) retroperitoneal lymph nodes < 2cm
   b) lung metastases; with < 5 lung metastases none >1cm
2) Eligible for and choses CRS and HIPEC upfront. Prior systemic therapy for colorectal cancer in the last 6 months.
3) DPYD variant detected.
4) MSI high.

5) Previous CRS or HIPEC.

Ovarian group only:

1) Extra-peritoneal metastases (with the exception of retroperitoneal lymph nodes)
2) Parenchymal liver or spleen metastases.
3) Malignant pleural effusion.
4) Non-epithelial pathology subtype.
5) Peritoneal disease, amenable to surgical resection.

Stomach group only:

1) Extra-peritoneal metastases (with the exception of retroperitoneal lymph nodes).
2) Prior systemic anti-cancer therapy, radiotherapy or surgery for stomach cancer.
3) Gastric or duodenal stent in-situ.
4) Gastro-oesophageal junction Siewert Type 1 or Type 2 tumour.
5) Symptoms and/or radiology suggestive of impending and/or current bowel obstruction.
6) Uncontrolled and persistent ascites.
7) MSI high.
8) DPYD variant detected.
9) Previous CRS or HIPEC.

9 Recruitment, screening and registration

9.1 Participant identification

Patients will be identified within registered NHS sites across the UK. Participants will be patients with PM from colorectal, ovarian or stomach cancer deemed potentially eligible at local multidisciplinary team (MDT) meetings.

Given the trial population it is anticipated that many of the investigations required to ascertain eligibility will have already been undertaken. All results available to the MDT will be used to conduct initial screening against the inclusion and exclusion criteria. Screening logs should be completed at this stage to include all those patients that fulfil eligibility criteria included those invited but not randomised into the trial. Further screening and final confirmation of eligibility will take place after the patient has agreed to participate and signed the trial Consent Form (CF).

Table 1: Screening requirements

Screening test	Timescale
Medical history and examination	Within 28 days prior to randomisation
Performance status assessment (ECOG)	Within 28 days prior to randomisation
Urine pregnancy test (if woman of childbearing potential (WOCBP)	Within 7 days prior to randomisation
Assessment of concomitant medications	Within 28 days prior to randomisation
CT scan with contrast (thorax, abdomen and pelvis)	Within 28 days prior to randomisation

Bloods: FBC, U&Es, LFTs, bone profile, DPYD testing*	Within 7 days prior to randomisation with the exception of DPYD testing which can be performed at any time prior to randomisation
Mismatch Repair (MMR) and / or MSI*, HER2** and CPS** testing on tumour biopsy	Any time prior to randomisation

** Applicable to colorectal and stomach groups only*
*** Applicable to stomach group only*

9.2 Screening logs

A screening log of all patients with:

- PM from primary adenocarcinoma of the colorectum for whom SACT is being considered
- PM from primary epithelial ovarian, tubal, or primary peritoneal platinum-resistant carcinoma for whom SACT is being considered
- PM from primary adenocarcinoma of stomach or Siewert type 3 gastro-oesophageal junction tumour for whom SACT is being considered

not consented or approached will be kept at each site so that any biases from differential recruitment will be detected. As much detail as possible should be recorded on the screening logs.

When at site, logs may contain identifiable information, but this **must be redacted** prior to being sent to the CTR. The screening log should be sent to PICCOS@cardiff.ac.uk on a monthly basis (see section 25 for further detail on data monitoring/quality assurance).

9.3 Informed consent

The patient's clinician will introduce the trial and offer them the opportunity to discuss it in more detail with a member of the local trial team. The nature of the trial, together with all procedures and risks will be fully explained to each prospective trial participant by one of the Investigators. Full details of the trial, in the form of a printed Participant Information Sheet (PIS), will be provided for the patient to take away and consider prior to giving their consent to participate. This will include a separate general anaesthetic PIS, produced by the Royal College of Anaesthetists, to ensure patients are clear that the PIPAC procedure involves a general anaesthetic and the associated risks of this.

The participant's written informed consent must be obtained using the trial Consent Form (CF), which follows the PIS. The potential participant should be given sufficient time after the initial invitation to participate before being asked to sign the CF (usually 24 hours). Informed consent must be obtained prior to the potential participant undergoing procedures that are specifically for the purposes of the trial, including any screening procedures described in Section 9.1 which are not done as standard. Initial consent to the trial must be taken by a medically qualified Investigator delegated the responsibility on the site delegation log by the local PI. Reconsent can be taken by anybody who has been appropriately trained and delegated the responsibility on the site delegation log by the local PI, unless indicated otherwise by the CTR. Guidance on use of remote re-consent for amendments will be given by the Sponsor at the time of amendment implementation. Please note, only when written informed consent has been obtained from the patient and they have been randomised into the trial can they be considered a trial participant.

Participants should always be asked to initial next to each statement and sign a CF. One copy should be given to the participant, but the original copy should be kept in the Investigator site file and a further copy should be kept with participant's hospital notes.

Participant specific consent is requested to collect their NHS number to utilise NHS data to monitor long-term health status.

Patients are asked if they would like to optionally consent to the collection of Formalin Fixed Paraffin Embedded (FFPE) tumour blocks, and provision of these to the PICCOS trial. FFPE tumour samples will be from initial diagnostic cancer biopsy and, for those in the intervention arm, routine biopsies taken at PIPAC surgeries. Optional consent will also be obtained for genetic analysis to be performed on these samples.

Optional consent is requested for CT scan images relating to the participant's disease, in addition to those produced as part of the trial, to be used for future ethically approved research.

The right of the participant to refuse to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the Investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

Consent Logs of all patients consented and reconsented to the trial must be kept in the ISF and forwarded to CTR upon request.

9.4 Randomisation

Participants will be randomised via the central PICCOS database. Sites should complete the first part of randomisation Case Report Form (CRF), answering all the questions before submitting the randomisation. Please note, you will need to input the patient's preferred PIPAC centre at the time of randomisation. Once the randomisation is completed, the database will confirm whether the participant has been allocated to the control or intervention arm. The allocation will be sent via email to those indicated as requiring it by the site. If the patient is allocated to receive PIPAC, the PIPAC site will also be notified.

The randomisation system can be accessed via: https://redcap.ctr.cardiff.ac.uk/redcap/

If the online system becomes unavailable for any reason, site staff should contact PICCOS@cardiff.ac.uk and a manual randomisation process will be initiated.

Following randomisation, participants should be provided with a Patient Card to identify them as PICCOS trial participants.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participant's care will not be affected at any time by declining to participate or withdrawing from the trial. Participants who withdraw from the trial will not be replaced by additional recruitment.

Withdrawal from the trial should not affect ongoing patient care, and patients should continue to receive best possible standard treatment.

If a participant initially consents but subsequently wishes to withdraw from an aspect(s) of the trial, clear distinction must be made as to what aspect(s) of the trial the participant is withdrawing from. These aspects could be:

1) SACT.
2) PIPAC alone.
3) PIPAC and SACT.
4) QoL questionnaires.
5) Trial-specific follow-up assessments / visits *(NB: routine follow-up assessments should continue as usual, and data collected from these can continue to be provided to the CTR unless participant also withdraws from this as per point +6).*
6) Collection of data from routine hospital notes (e.g. OS data) that does not require the participant to attend any further hospital visits for trial purposes.
7) Qualitative sub-study (if applicable)
8) Consent for tissue biopsy(ies) of tumour taken as part of participant's routine care either when they were first diagnosed with colorectal / ovarian / stomach cancer or at a subsequent surgery to be sent to collaborating laboratories for analysis.
9) Consent for CT scan images pertaining to their cancer (additional to those obtained for trial purposes) to be used for future ethically approved research.
10) Consent for their NHS number to be used to monitor long term health status.
11) All of the above.

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal and as such it will not be deleted. Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the PIS but, in brief: If a participant wishes to stop taking part in the trial completely, they will need to be seen one last time for an assessment and tests. If the participant is suffering a serious reaction to the trial treatment when they decide to stop, you will need to continue to collect information about them for as long as the reaction lasts.

A participant may discontinue or be discontinued from trial treatment by their investigator for the following reasons:

- Intolerance to trial medication.
- Severe surgical complications.
- Withdrawal of consent for treatment by the participant.
- Any alteration in the participant's condition which justifies the discontinuation of the treatment in the Investigator's opinion (other than peritoneal progression, as these constitute an endpoint) e.g., inability to perform laparoscopy.
- Pregnancy.
- Non-compliance.

NB: Any patient in the intervention arm identified as having peritoneal disease progression will have no further PIPAC surgical interventions but should not be considered as having withdrawn from the trial for this reason.

If a participant discontinues trial treatment prior to the scheduled end of treatment in the protocol, the investigator should ensure that this withdrawal from trial treatment is recorded ASAP on the Withdrawal CRF on the REDCap database. It is best practise to discuss with the participant at this time whether they are happy to continue with other trial activities, however this conversation can happen at a later date.

Participants who consent and subsequently withdraw to their tumour samples being sent to a laboratory for analysis should be asked to complete a **PICCOS Participant Withdrawal Consent Form**. The information provided on this form should be used to subsequently complete the Withdrawal CRF on the REDCap database to inform the CTR. The Participant Withdrawal Consent Form should not be submitted to the CTR.

In all cases where a participant stops trial treatment early or withdraws from another aspect of the trial, any discussions held with the participant regarding their withdrawal, and aspect(s) of the trial they no longer wish to continue with should be recorded within the patient's medical notes. . Any queries relating to potential withdrawal of a participant should be forwarded to PICCOS@cardiff.ac.uk.

10.2 Lost to follow up

Patients will be considered lost to follow-up if they stop attending trial follow-up visits before the primary or secondary outcome data have been collected or the trial has completed data collection.

Missing data will be collected via routine NHS data.

Outcome data from participants who deviate from the protocol will be collected.

11 Trial Intervention

11.1 Treatments

Prior to randomisation, the treating Investigator will select the SACT regimen most appropriate to the individual patient from the options available in the protocol for the patient's disease group.

Following randomisation, treatment should commence within 2 weeks for all groups other than the ovarian intervention arm, for whom first PIPAC should take place within 3 weeks. Once treatment commences, patients should be provided with a Patient Card, to identify them as participants in the PICCOS trial in case of emergency.

Colorectal group treatment

Figure 2: Colorectal group treatment schema

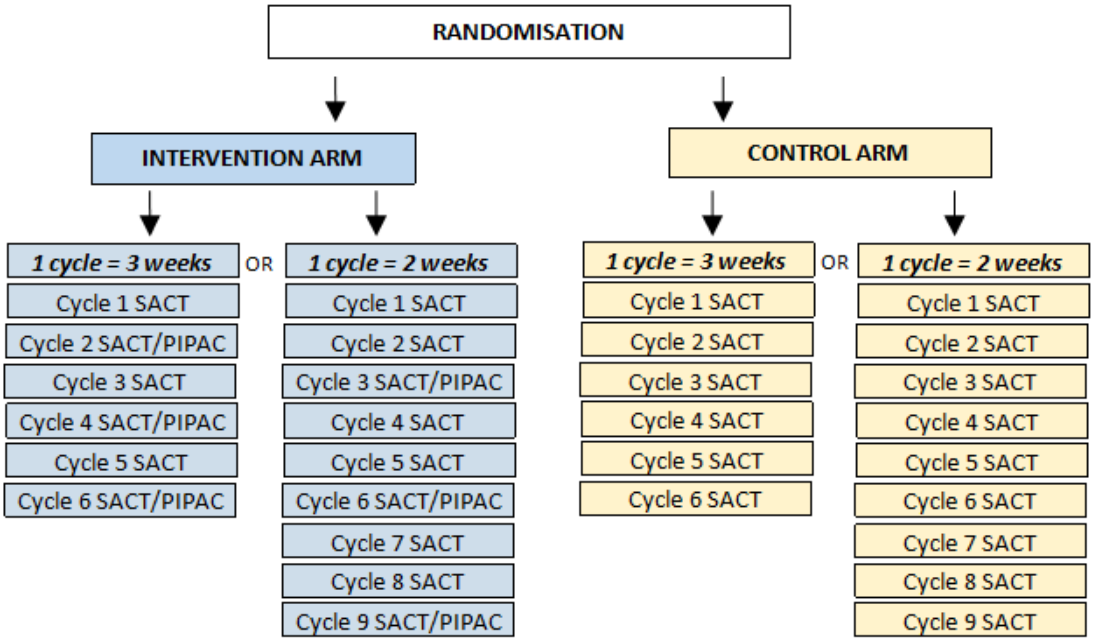


Table 2: Colorectal group dosing schedule

Option No. Cycle length	Control arm- Colorectal	Intervention arm- Colorectal	
	SACT	**SACT**	**PIPAC chemotherapy**
Option 1 = FOLFOX 2 weekly cycles	On day 1 of each cycle: *(9 cycles total)* • Oxaliplatin 85mg/m^2 IV • Fluorouracil (5FU) 400mg/m^2 IV bolus • 5FU 2400mg/m^2 continuous IV infusion • Sodium folinate 350mg IV infusion OR calcium folinate 300 or 350mg IV infusion	On day 1 of cycles where PIPAC is not given: FOLFOX • Oxaliplatin 85mg/m^2 IV • 5FU 400mg/m^2 IV bolus • 5FU 2400mg/m^2 continuous IV infusion • Sodium folinate 350mg IV infusion OR calcium folinate 300 or 350mg IV infusion On cycles 3, 6, 9 where PIPAC is also given: • 5FU 2400mg/m^2 continuous IV infusion should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC	On cycles 3, 6 and 9 • Oxaliplatin 120mg/m^2 IP (dose reduction to 90mg/m^2 for participants with frailty, intolerance, or neuropathy as agreed by site oncologist) OR • Mitomycin C 7.5mg/m^2 IP *(if contraindication to Oxaliplatin)* *PIPAC should be scheduled day 3 to day 7 of the cycles to ensure a break of 24 hours between finishing the 5FU infusion and having PIPAC. If it is not possible to schedule the 5FU infusion prior to a participant's PIPAC it can be administered 48 hours or more after the PIPAC* Subsequent non PIPAC cycles should occur a minimum of 10 days after completion of the 5FU infusion.
Option 2 = FOLFOX + cetuximab 2 weekly cycles	Each cycle: *(9 cycles total)* • FOLFOX (as in option 1) • Cetuximab 500mg/m^2 IV day 1	On day 1 of cycles where PIPAC is not given: • FOLFOX (as in option 1) • Cetuximab 500mg/m^2 IV day 1 On cycles 3, 6, 9 where PIPAC is also given: • 5FU 2400mg/m^2 continuous IV infusion should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC • Cetuximab 500mg/m^2 IV infusion	Cycles 3, 6 and 9: oxaliplatin or mitomycin as in option 1

Option No. Cycle length	Control arm- Colorectal	Intervention arm- Colorectal	
	SACT	**SACT**	**PIPAC chemotherapy**
Option 3 = FOLFOX + Panitumumab 2 weekly cycles	Each cycle: *(9 cycles total)* • FOLFOX (as in option 1) • Panitumumab 6mg/Kg IV day 1	On day 1 of cycles where PIPAC is not given: • FOLFOX (as in option 1) • Panitumumab 6mg/Kg IV day 1 On cycles 3, 6, 9 where PIPAC is also given: • 5FU 2400mg/m^2 continuous infusion • Panitumumab 6mg/Kg IV infusion	Cycles 3, 6 and 9: oxaliplatin or mitomycin as in option 1
Option 4 = FOLFIRI 2 weekly cycles	On day 1 of each 2 week cycle: *(9 cycles total)* • Irinotecan 180mg/m^2 IV infusion • 5FU 400mg/m^2 IV bolus • 5FU 2400mg/m^2 continuous IV infusion • Sodium folinate 350mg IV infusion OR calcium folinate 300 or 350mg IV infusion	On day 1 of cycles where PIPAC is not given: FOLFIRI • Irinotecan 180mg/m^2 IV infusion • 5FU 400mg/m^2 IV bolus • 5FU 2400mg/m^2 continuous IV infusion • Sodium folinate 350mg IV infusion OR calcium folinate 300 or 350mg IV infusion On cycles 3, 6, 9 where PIPAC is also given: • 5FU 2400mg/m^2 continuous IV infusion should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC	Cycles 3, 6 and 9: oxaliplatin or mitomycin as in option 1
Option 5 = FOLFIRI + Cetuximab 2 weekly cycles	Each cycle: *(9 cycles total)* • FOLFIRI (as in option 4) plus • Cetuximab 500mg/m^2 IV day 1	On day 1 of cycles where PIPAC is not given: • FOLFIRI (as in option 4) • Cetuximab IV 500mg/m^2 IV day 1 On cycles 3, 6, 9 where PIPAC is also given: • 5FU 2400mg/m^2 continuous IV infusion should be administered with pump disconnection 24 hours	Cycles 3, 6 and 9: oxaliplatin or mitomycin as in option 1

Option No. Cycle length	Control arm- Colorectal	Intervention arm- Colorectal	
	SACT	**SACT**	**PIPAC chemotherapy**
		pre PIPAC or pump attachment 48 hours after PIPAC • Cetuximab IV 500mg/m^2 IV infusion	
Option 6 = FOLFIRI + Panitumumab 2 weekly cycles	Each cycle: *(9 cycles total)* • FOLFIRI (as in option 4) plus • Panitumumab 6mg/Kg IV day 1	On day 1 of cycles where PIPAC is not given: • FOLFIRI (as in option 4) • Panitumumab 6mg/Kg IV day 1 On cycles 3, 6, 9 where PIPAC is also given: • 5FU infusion 2400mg/m^2 continuous infusion should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC • Panitumumab 6mg/Kg IV	Cycles 3, 6 and 9: oxaliplatin or mitomycin as in option 1
Option 7 = CAPOX 3 weekly cycles	Each 3 week cycle: *(6 cycles total)* • Oxaliplatin 130mg/m^2 IV day 1 • Capecitabine 1000mg/m^2 bd for 14 days (days 1-14 of the cycle) PO	On cycles where PIPAC is not given: • Oxaliplatin 130mg/m^2 IV day 1 • Capecitabine 1000mg/m^2 bd for 14 days (days 1-14 of the cycle) PO On cycles where PIPAC is given: • Capecitabine 1000mg/m^2 bd for 14 days (days 1-14 of the cycle) PO. *Capecitabine should be omitted for 24 hours prior to the PIPAC procedure and for 48 hours afterwards. Missed tablets should not be replaced (thus only 11 days of tablets are required)*	Cycles 2, 4 and 6: • Oxaliplatin 120mg/m^2 IP (dose reduction to 90mg/m^2 for frail participants or those with neuropathy as agreed by site oncologist) OR • Mitomycin C 7.5mg/m^2 IP *(if contraindication to oxaliplatin* Subsequent non PIPAC cycles should occur a minimum of 6 days after completion of the last capecitabine tablets
In all cases dose reductions from prior cycles will be maintained			

Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.

Ovarian group treatment

Figure 3: Ovarian group treatment schema

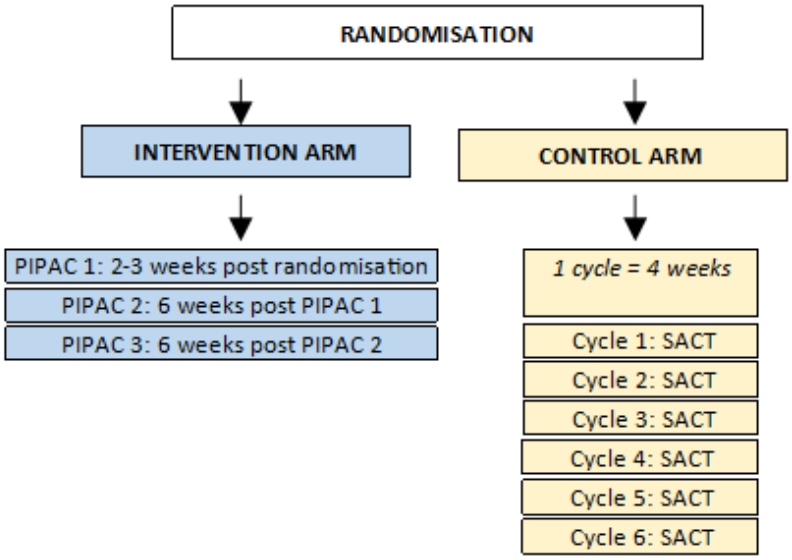


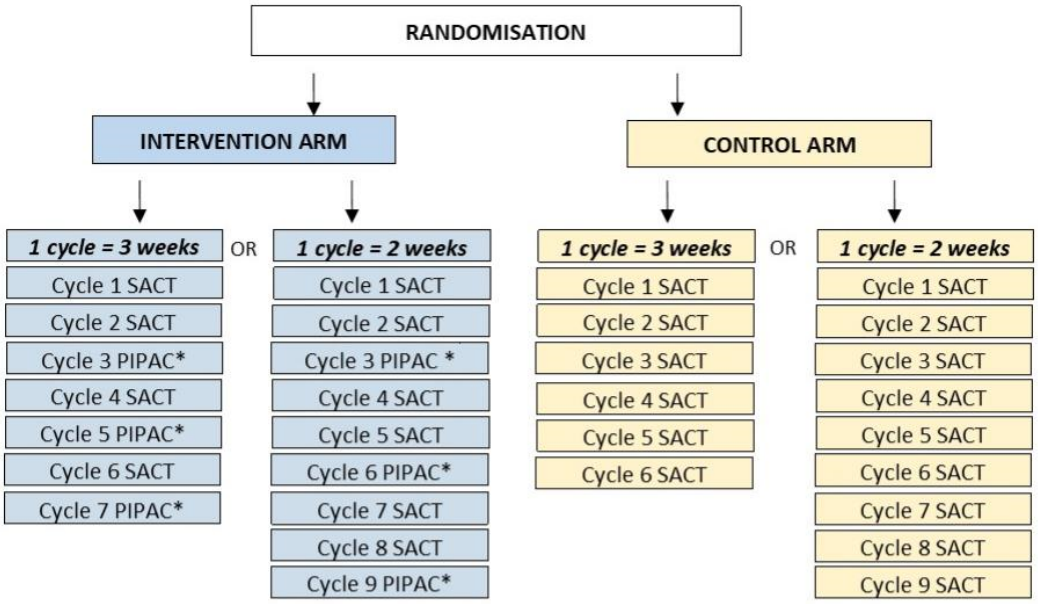
Table 3: **Ovarian group dosing schedule**

Option No **Cycle length**	**Control arm - Ovarian** **SACT**	**Intervention arm- Ovarian** **SACT**	 **PIPAC chemotherapy**
Option 1 *4 weekly cycles*	On days 1, 8, 15 of each 4 week cycle: (6 cycles total) • Paclitaxel 80mg/m^2 IV infusion	None	PIPAC 1: 2-3 weeks after randomisation PIPAC 2: PIPAC 1 + 6 weeks PIPAC 3: PIPAC 2 + 6 weeks • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP
Option 2 *4 weekly cycles*	On days 1, 8, 15, 22 of each 4 week cycle: (6 cycles total) • Paclitaxel 80mg/m^2 IV infusion	None	As in option 1
Option 3 *4 weekly cycles*	On day 1 of each 4 week cycle: (6 cycles total) • Liposomal doxorubicin 40 - 50mg/m^2 IV infusion	None	As in option 1

Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime in the control arm or have SACT added in, in the intervention arm, at the discretion of their treating PI. If chemotherapy is added to intervention arm, it should be completed 7 days prior to the PIPAC procedure.

Stomach group treatment

Figure 4: Stomach group treatment schema



**Trastuzumab/nivolumab/pembrolizumab (if applicable) should be continued during PIPAC cycles to maintain standard schedule*

*** Trastuzumab/nivolumab/pembrolizumab maintenance should continue after completion of trial schema as per standard of care (if clinically indicated).*

**** Maintenance cytotoxic chemotherapy is not permitted in the gastric arm of the trial*

Table 4: Stomach group dosing schedule

NB: In all cases dose reductions from prior cycles will be maintained

Option No, *Cycle length*	**Control arm- Stomach**	**Intervention arm- Stomach**		
	SACT	**SACT**	**PIPAC chemotherapy**	**Comments**
HER 2 negative patients:				
Option 1 = FOLFOX 2 weekly cycles	On day 1 of each 2 week cycle: *(9 cycles total)* • Oxaliplatin 85mg/m^2 IV • 5FU 400mg/m^2 IV bolus • 5FU 2400mg/m^2 continuous IV infusion • Sodium folinate 350mg IV OR calcium folinate 300 or 350mg IV infusion	On day 1 of each 2 week cycle: where PIPAC is not given *((IV SACT is OMITTED during PIPAC cycles (i.e. cycle 3, 6 and 9)):* • Oxaliplatin 85mg/m^2 IV • 5FU 400mg/m^2 IV bolus • 5FU 2400mg/m^2 IV continuous infusion • Sodium folinate 350mg IV OR calcium folinate 300 or 350mg IV infusion	Cycles 3, 6 and 9 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP	
Option 2 = CAPOX 3 weekly cycles	Each 3 week cycle: *(6 cycles total)* • Oxaliplatin 130mg/m^2 IV day 1 • Capecitabine 1000mg/m^2 PO days 1-14 bd	Each 3 week cycle where PIPAC is not given *((IV and oral SACT is OMITTED during PIPAC cycles (i.e. cycle 3,5 and 7)):* • Oxaliplatin 130mg/m^2 IV day 1 • Capecitabine 1000mg/m^2 PO days 1-14 bd	Cycles 3, 5 and 7 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC.
Option 3 = CX 3 weekly cycles	Each 3 week cycle: *(6 cycles total)* • Cisplatin 60mg/m^2 IV day 1	Each 3 week cycle where PIPAC is not given *(IV and oral SACT is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7)):* • Cisplatin 60mg/m^2 IV day 1	Cycles 3, 5 and 7 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC.

Option No, *Cycle length*	Control arm- Stomach	Intervention arm- Stomach		
	SACT	**SACT**	**PIPAC chemotherapy**	**Comments**
	• Capecitabine 1000mg/m^2 PO days 1-14 bd	• Capecitabine 1000mg/m^2 PO days 1-14 bd	• Doxorubicin 2.1mg/m^2 IP	
HER 2 positive patients:				
Option 4 = CXtraz 3 weekly cycles Trastuzumab to be used as per current NICE recommendation	Each 3 week cycle: *(6 cycles total)* • CX as per option 3 • Trastuzumab* IV day 1, cycle 1 8mg/kg, subsequent cycles 6mg/kg.	On day 1 of each 3 week cycle where PIPAC is not given *(IV and oral chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7)):* • CX as per option 3 In addition, on day 1 of every 3 week cycle: • Trastuzumab IV, cycle 1 8mg/kg, subsequent cycles 6mg/kg. Trastuzumab should be continued throughout PIPAC cycles and given within 3 days* post PIPAC, allowing interval of 24 hours between PIPAC and trastuzumab.	Cycles 3, 5 and 7 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP	Trastuzumab should be continued 3 weekly throughout PIPAC. Allow at least 24h interval between PIPAC and trastuzumab in case of complications e.g. acute pancreatitis or allergic reaction. Maintenance trastuzumab may be continued upon completion of planned trial treatment (if clinically indicated).
Option 5 = CAPOXtraz 3 weekly cycles Trastuzumab to be used as per current	Each 3 week cycle: *(6 cycles total)* • CAPOX as in option 2 • Trastuzumab* IV day 1, cycle 1 8mg/kg, subsequent cycles 6mg/kg.	Each 3 week cycle where PIPAC is not given *(* IV and oral chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7)*):* • CAPOX as in option 2 In addition, on day 1 of every 3 week cycle:	Cycles 3, 5 and 7 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC. Allow at least 24h interval between PIPAC and trastuzumab in case of complications e.g. acute pancreatitis or allergic reaction.

Option No, *Cycle length*	Control arm- Stomach	Intervention arm- Stomach		
	SACT	**SACT**	**PIPAC chemotherapy**	**Comments**
NICE recommendation		• Trastuzumab IV day, cycle 1 8mg/kg, subsequent cycles 6mg/kg. Trastuzumab should be continued throughout PIPAC cycles and given within 3 days* post PIPAC, allowing interval of 24 hours between PIPAC and trastuzumab		Maintenance trastuzumab may be continued upon completion of planned trial treatment (if clinically indicated).
Option 6 = FOLFOXtraz 2 weekly cycles Trastuzumab to be used as per current NICE recommendation	On day 1 of each 2 week cycle: *(9 cycles total)* • FOLFOX as per option 1 PLUS 3 weekly • Trastuzumab* IV, cycle 1 8mg/kg, subsequent cycles 6mg/kg.	On day 1 of each 2 week cycle where PIPAC is not given *(* IV chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 6 and 9)*):* • FOLFOX as per option 1 In addition, on day 1 every 21 days: • Trastuzumab IV, cycle 1 8mg/kg, subsequent cycles 6mg/kg Trastuzumab should be continued throughout PIPAC cycles and given within 3 days* post PIPAC, allowing interval of 24 hours between PIPAC and trastuzumab.	Cycles 3, 6 and 9 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP	Allow at least 24h interval between PIPAC and trastuzumab in case of complications e.g. acute pancreatitis or allergic reaction Maintenance trastuzumab may be continued upon completion of planned trial treatment (if clinically indicated)
Patients eligible for immunotherapy in line with current NICE recommendations (currently HER –2 negative, CPS ≥5)				

Option No, *Cycle length*	Control arm- Stomach	Intervention arm- Stomach		
	SACT	**SACT**	**PIPAC chemotherapy**	**Comments**
Option 7 = CAPOXniv 3 weekly cycles Nivolumab to be used as per current NICE recommendation	Each 3 week cycle: *(6 cycles total)* • CAPOX as in option 2 • Nivolumab** 360mg IV day 1	Each 3 week cycle where PIPAC is not given *(IV and oral chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7):* • CAPOX as in option 2 In addition, on day 1 of each 3 week cycle: • Nivolumab 360mg IV Nivolumab should be continued throughout PIPAC cycles (if scheduled), and given within 3 days* post PIPAC, allowing interval of 24 hours between PIPAC and nivolumab.	Cycles 3, 5 and 7 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC. Nivolumab should be continued 3 weekly throughout PIPAC cycles. Allow at least 24h interval between PIPAC and nivolumab in case of complications e.g. acute pancreatitis or allergic reaction. Maintenance nivolumab may be continued upon completion of planned trial treatment (if clinically indicated)
Option 8 – FOLFOXniv 2 weekly cycles Nivolumab to be used as per current NICE recommendation	On day 1 of each 2 week cycle: *(9 cycles total)* • FOLFOX as per option 1 • Nivolumab** 240mg IV	On day 1 of each 2 week cycle where PIP)AC is not given *(IV chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 6 and 9)*: • FOLFOX as per option 1 In addition, on day 1 of each 2 week cycle: • Nivolumab 240mg IV Nivolumab should be continued throughout PIPAC cycles (if scheduled), and given within 3 days* post PIPAC,	Cycles 3, 6 and 9 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP	Nivolumab should be continued throughout PIPAC cycles. Allow at least 24h interval between PIPAC and nivolumab in case of complications e.g. acute pancreatitis or allergic reaction Maintenance nivolumab may be continued upon completion of planned trial treatment (if clinically indicated)

Option No, *Cycle length*	Control arm- Stomach	Intervention arm- Stomach		
	SACT	**SACT**	**PIPAC chemotherapy**	**Comments**
		allowing interval of 24 hours between PIPAC and nivolumab		
Option 9= CAPOXpembro 3 weekly cycles (CAPOX) Pembrolizumab to be used as per current NICE recommendation	Each 3 week cycle (6 cycles total) • CAPOX as in option 2 In addition, either (according to site preference): • On day 1, every 21 days, 200mg pembrolizumab IV OR • On day 1 every 42 days, 400mg pembrolizumab IV	Each 3 week cycle where PIPAC is not given *(IV and oral chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7):* • CAPOX as in option 2 In addition, either (according to site preference): • On day 1, every 21 days, 200mg pembrolizumab IV OR • On day 1 every 42 days, 400mg pembrolizumab IV Pembrolizumab should be continued throughout PIPAC cycles (if scheduled) and given within 3 days* post PIPAC, allowing interval of 24 hours between PIPAC and pembrolizumab.	Cycles 3, 5 and 7 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP	Allow at least 24h interval between PIPAC and pembrolizumab in case of complications e.g. acute pancreatitis or allergic reaction. Maintenance pembrolizumab may be continued upon completion of planned trial treatment (if clinically indicated).
Option 10 = FOLFOXpembro	On day 1 of each 2 week cycle (9 cycles in total) • FOLFOX as per option 1	On day 1 of each 2 week cycle where PIPAC is not given *(IV chemotherapy is OMITTED during PIPAC cycles i.e. cycle 3, 6 and 9):* • FOLFOX as per option 1	Cycles 3, 6 and 9 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP	Allow at least 24h interval between PIPAC and pembrolizumab in case of complications e.g. acute pancreatitis or allergic reaction.

Option No, *Cycle length*	Control arm- Stomach	Intervention arm- Stomach		
	SACT	**SACT**	**PIPAC chemotherapy**	**Comments**
2 weekly cycles (FOLFOX) Pembrolizumab to be used as per current NICE recommendation	In addition, either (according to site preference): • On day 1, every 21 days, 200mg pembrolizumab IV OR • On day 1 every 42 days, 400mg pembrolizumab IV	In addition, either (according to site preference): • On day 1, every 21 days, 200mg pembrolizumab IV OR • On day 1 every 42 days, 400mg pembrolizumab IV Pembrolizumab should be continued throughout PIPAC cycles (if scheduled) and given within 3 days* post PIPAC, allowing interval of 24 hours between PIPAC and pembrolizumab.	• Doxorubicin 2.1mg/m^2 IP	Maintenance pembrolizumab may be continued upon completion of planned trial treatment (if clinically indicated).

<u>In all cases dose reductions from prior cycles will be maintained</u>

Note:

- *Trastuzumab/ nivolumab / pembrolizumab (if applicable) should be continued during PIPAC cycles to maintain standard schedule (given within 3 days post PIPAC (a further +1 day is acceptable for scheduling purposes), allowing an interval of 24 hours between PIPAC and HER-2 therapy / immunotherapy).
- HER-2 directed therapy and immunotherapy allowed within their respective NICE recommendations.
- IV and oral cytotoxic chemotherapy is omitted during PIPAC cycles in the intervention arm.
  If using a 3 weekly capecitabine containing regimen, a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC.
- If using a pembrolizumab containing regime, 3 weekly or 6 weekly pembrolizumab is permitted. 6 weekly pembrolizumab may help with scheduling.
- If trastuzumab is delayed, please follow appropriate re-loading guidance.

- In the event that PIPAC does not go ahead on day 1 as planned, a +7 day window is allowed for PIPAC to be given before the next SACT needs to be deferred. If nivolumab or trastuzumab are given within 3 days post a deferred PIPAC cycle, the site is encouraged to give the nivolumab or trastuzumab as close as possible to the date next due (2 weeks later for 2 weekly nivolumab and 3 weeks later for 3 weekly nivolumab/pembrolizumab/ trastuzumab), recognising that this will lead to a disconnection between the cytotoxic SACT and the biological agent.
- Trastuzumab / nivolumab / pembrolizumab maintenance should continue after completion of trial schema (if clinically indicated) as per standard of care.
- Maintenance cytotoxic chemotherapy post-completion of trial schema is not permitted in the stomach arm of the trial.
- Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime in listed in the protocol at the discretion of their treating PI.

11.2 Treatment supply and storage (all disease groups)

No specific drug provision is necessary for the trial. All Investigational Medicinal Products (IMPs) and nIMPs (non-Investigational Medicinal Products) will be obtained through normal hospital supply routes. For SACT IMP and nIMPs these can also be sourced using pre-made bags of chemotherapy outsourced locally.

All IMPs and nIMPs should be stored as per current Summary Product Characteristics (SmPC). Intraperitoneal (IP) IMPs should be prepared as described in the Protocol and PICCOS Pharmacy Manual. IMPs given as per SmPC (paclitaxel and liposomal doxorubicin), and all n-IMPs, should be prepared as per SmPC.

Once prepared drugs to be given IP should be kept at appropriate storage conditions and used with the recommended time based on site specific approved stability data.

Any temperature deviations following dispensing, for both IMPs and nIMPs, should be dealt with as per SmPC and PICCOS Pharmacy Manual.

More information can be found in the PICCOS Pharmacy Manual.

11.3 Treatment prescribing and dispensing (all disease groups)

SACT and PIPAC chemotherapy will be prescribed at the doses described in section 11.1.

SACT will be prepared as per local standard practice.

The trial prescription form will be used to request the trial drug(s) from pharmacy on an individual participant basis. Prescriptions can be completed by staff permitted to do so as per local practice.

Body surface area (BSA) should be calculated using the site's usual method.

To assess PIPAC doses creatinine clearance (CrCl) should be calculated using the online ClinCalc calculator: https://clincalc.com/kinetics/crcl.aspx as this calculator automatically accounts for inaccuracies that extremes of body weight can lead to.

Local policy can be followed in how renal function is assessed in order to assess doses of SACT.

Dose banding as per NHSE dose banding table is allowed for SACT IMP and nIMP. The NHSE dose banding tables do not apply to doses delivered via PIPAC. However, PIPAC doses can be rounded to nearest whole number.

PIPAC chemotherapy will be assembled by a chemotherapy pharmacist on an individual patient basis. This will require preparation of the chemotherapy at the specified dose in the solution specified in Table 5. Chemotherapy can either be prepared in an IV bag or into the appropriate syringe(s) by pharmacy. If assembled into syringe(s), the chemotherapy will be placed in a sealed and labelled plastic bag ready for transport to theatre. If assembled into an IV bag, this will be labelled and transported to theatre, where the surgeon will spike the IV bag and draw the chemotherapy into the appropriate syringe(s) immediately prior to administration to the patient. For labelling requirements see section 11.14.

Table 5: PIPAC preparation details

Chemotherapy	Dose	Dilution solution	Volume of dilution solution
Oxaliplatin*	120mg/m^2	5% dextrose	150-200 ml
Oxaliplatin	90 mg/m^2	5% dextrose	150-200 ml
Mitomycin C	7.5 mg/m^2	NaCl 0.9%	50ml

Chemotherapy	Dose	Dilution solution	Volume of dilution solution
Cisplatin	10.5 mg/m^2	NaCl 0.9%	150ml
Doxorubicin	2.1 mg/m^2	NaCl 0.9%	50ml

*In patients for whom the 120mg/m^2 dose of oxaliplatin IP is intended, it may not be possible for them to receive the full intended dose if they have a high BSA due to restrictions on oxaliplatin concentration as a consequence of stability data for the container that the prepared chemotherapy will be stored in. These patients can still have PIPAC but a slightly lower dose will need to be prepared/given in order to accommodate the stability data and the volume of the syringe used for PIPAC (200ml).

11.4 Drug administration

SACT

SACT should be administered according to section 11.1 and as per local practice.

PIPAC procedure – all groups

PIPAC will be performed in line with the ISSPP training that PIPAC centres have received in order to participate in the trial and as specified in the PICCOS PIPAC Manual. The PICCOS PIPAC safety checklist must be completed alongside each PIPAC procedure.

The PIPAC procedure is repeated three times as per the schedule in section 11.1

11.5 Delays

SACT

If a participant tests positive for Covid-19, SACT should be delayed as per local standard practice. If SACT is delayed, subsequent cycles should also be delayed to maintain treatment timelines (i.e. if delayed by 1 week, all subsequent cycles and follow-up visits should be delayed by 1 week, CT scans should be maintained as per schedule of assessments and not moved).

PIPAC

PIPAC can be delayed if patient does not meet minimum criteria for surgery. If PIPAC is delayed for 3 weeks or longer (other than for Covid-19 infection, as noted below), discussions should be had with the PICCOS trial team on whether appropriate to continue treatment.

If a participant in the intervention arm tests positive for Covid-19, PIPAC should be delayed as per local standard practice for surgery.

If PIPAC is delayed, subsequent treatment cycles and PIPACs should also be delayed to maintain treatment timelines (i.e. if delayed by 1 week, all subsequent treatments and follow-up visits should be delayed by 1 week, CT scans should be maintained as per schedule of assessments and not moved).

11.6 Dose modification for toxicity

SOC systemic SACT can be modified as permitted within the SmPC and in accordance with local practice. However, full doses as stipulated in the protocol must be given for cycle 1.

A dose reduction to IP oxaliplatin (colorectal group PIPAC) from 120mg/m^2 to 90mg/m^2 is permitted for participants with frailty, neuropathy (as per ISSPP PIPAC Consensus Statement, March 2022 (71)) or intolerance subject to discussion and agreement of site oncologist.

There are no dose modifications for IP cisplatin, doxorubicin or mitomycin.

Safety signals from trial drugs will be regularly monitored throughout the course of the trial. If excessive toxicity is observed from the PIPAC drugs, a protocol amendment to introduce the possibility of a standard dose reduction will be considered.

Colorectal group participants who show toxicity that in the view of their treating Investigator warrants stopping oxaliplatin, can be treated with mitomycin at their subsequent scheduled PIPAC cycle.

Ovarian or stomach group participants who show toxicity that in the view of their treating Investigator warrants stopping either cisplatin or doxorubicin can be treated at their subsequent scheduled PIPAC cycle with the other drug alone.

11.7 Management of toxicity and hypersensitivity reactions

Toxicity and hypersensitivity reactions to SACT and PIPAC chemotherapy should be managed as per standard anaphylaxis protocol. Following hypersensitivity reactions, any further surgeries should be discussed with the trial team prior to being undertaken.

11.8 Management of overdose/ underdose

In the event of an overdose/underdose of any drug provided within PICCOS, any further treatment should be withheld and the PICCOS Trial Manager should be notified via a dosing error form being completed and submitted to PICCOS@cardiff.ac.uk within 24 hours of site becoming aware. Treatment should not recommence until advice has been obtained from the Sponsor and CI / disease site lead as required. This does not need to be reported as an adverse event but if the patient experiences a Serious Adverse Event (SAE) that the PI considers may be causally related to the overdose/underdose then this must be clearly stated on a SAE form submitted to the CTR Pharmacovigilance (PV) team. Please see section 14 for more information on reporting SAEs.

If a patient is underdosed due to reasons not related to toxicity then a dosing error form should be completed. If doses are stopped prematurely or otherwise reduced due to toxicity then this is captured on the CRF.

11.9 Pre-medication

Pre-medication should be prescribed as per local guidance.

11.10 Prohibited medications and interaction with other drugs

Prohibited medications

Drugs described as contraindicated in the SmPC for each SACT or chemotherapy agent will not be permitted. The most up to date SmPC from www.medicines.org.uk will be used. Treatment with any other anti-cancer experimental drug/ agent is not permitted for the duration of the trial.

Bevacizumab and aflibercept is prohibited to be given whilst receiving trial treatment and for 4 weeks after completion of trial treatment. Please note a 4-week washout period should be allowed prior to randomisation as per trial exclusion criteria.

Medications permitted with caution / procedures

Other medications, as long as they are not anti-cancer or experimental drugs/ agents, will be permitted in line with the SmPC for each drug. The most up to date SmPC from www.medicines.org.uk will be used.

In the event of a possible disease response to the point that reductive surgery may be an option for the patient, this will be permitted.

11.11 Permitted concomitant medications

GCSF (Granulocyte colony-stimulating factor) should be prescribed as per local guidance and should be used as required.

11.12 Supportive care

Supportive medications should be prescribed as per local guidance and should be used as required.

11.13 Accountability procedures

Since the trial will use standard chemotherapies already available at pharmacy, there will be no trial specific drug delivery to site.

- Trial specific per-participant accountability logs should be maintained for all IP IMPs.
- No trial specific additional accountability is required for the IV IMPs. Standard aseptic dispensing worksheets can be used for trial specific accountability purposes. For sites that do not have standard aseptic dispensing worksheets, trial specific simple accountability logs have been produced and can be used.
- No trial specific accountability records will be required for nIMPs.

The PICCOS trial team will provide a template for the per participant accountability logs, but local templates can be used within the trial provided all required information is collected.

Any drug recalls should be actioned as per local practice.

For further information, refer to the PICCOS Pharmacy Manual.

11.14 Drug labelling

All IMPs- oxaliplatin (IP), mitomycin (IP), cisplatin (IP), doxorubicin (IP), paclitaxel (IV) and liposomal doxorubicin (IV): IP syringes/ IV bags should be labelled with full information regarding the trial in accordance with EU Good Manufacturing Process (GMP) Annex 13, as per Sponsor provided labels.

nIMPs- capecitabine (PO), oxaliplatin (IV), calcium folinate (IV), nivolumab (IV), sodium folinate (folinic acid) (IV), trastuzumab (IV), 5FU (IV), irinotecan (IV), cisplatin (IV), cetuximab (IV), panitumumab (IV) and pembrolizumab (IV): There is no requirement to add trial specific labels to packs of these drugs.

All labels are included in the Pharmacy File provided by CTR upon site activation. For further information refer to the PICCOS Pharmacy Manual.

11.15 Drug disposal

SACT

Unused SACT drugs should be disposed of as per local practice.

PIPAC chemotherapy

Prepared chemotherapy delivered to surgery for use in PIPAC procedures whether partially used / not used for any reason should be disposed of in theatre in appropriate cytotoxic bins in accordance with local policy and procedures. The gas inside the abdomen at the end of the PIPAC procedure will require disposal as per the PIPAC Manual. It will be evacuated from the abdomen via a closed secure system. All consumables and waste from theatre after PIPAC has been performed will be packed and labelled as per local guidelines for chemotherapy waste/ PIPAC Manual.

12 Sample management

Participants are asked to optionally consent to the collection of Formalin Fixed Paraffin Embedded (FFPE) tumour blocks, and for the provision of these to the PICCOS trial. FFPE tumour blocks can be from a participant's initial diagnostic cancer biopsy and, for those in the intervention arm, any routine biopsies taken at PIPAC surgeries. Consent will also be obtained for genetic analysis to be performed on these samples.
All samples should be stored locally/ in local biobanks until requested by the PICCOS trial team. All sites are encouraged to collect these samples, but this is not currently mandatory.

13 Trial procedures

13.1 Assessments

Schedule of Assessments vary depending on disease type and SACT regime to be given. The Appendix (section 16.1) includes all schedules.

Baseline assessments- all participants

Table 6 summarises the assessments which should be performed prior to commencing any trial treatment along with the required timeframes.

Table 6: Baseline Assessments

Assessment	Timepoint
Bloods: assessment of tumour markers (CEA for colorectal / CA125 for ovarian group)	Within 4 weeks prior to day 1 of cycle 1
Ethnicity documentation	After trial consent but prior to first cycle of SACT or PIPAC
Quality of life questionnaire	After trial consent but prior to first cycle of SACT or PIPAC

Assessments prior to each cycle of SACT

Table 7 summarises the assessments which should be performed prior to each SACT cycle within the timeframes described. Where a participant has their screening bloods done within 2 weeks of starting SACT these do not need to be repeated at cycle 1. With the exception of bloods, where screening assessments fit within the timeframes included in table 7 there is no requirement to repeat the assessment pre cycle 1 of SACT.

Table 7: Assessments required prior to each SACT cycle

Assessment	Timepoint
Physical assessment (including height (cycle 1 only), weight)	Within 72 hours, or as per local practice

Assessment	Timepoint
Vital signs (including blood pressure, heart rate)	Within 72 hours, or as per local practice
Bloods* (including FBC, U&Es, Mg^{2+}, LFTs, bone profile)	Within 72 hours, or as per local practice
Adverse Events (AE)/ SAEs	During the PV reporting period
Concomitant medications	Within 72 hours, or as per local practice
ECOG performance status assessment	Within 72 hours, or as per local practice
Assessment of tumour marker (CA125 for ovarian patients, CEA for colorectal patients, not applicable to stomach patients)	Within 72 hours, or as per local practice
Documentation of episodes of therapeutic ascitic drainage since randomisation/last treatment cycle. *Ovarian group only*	Ideally within 72 hours

**Thyroid function tests and random blood glucose testing should be performed prior to each cycle for patients on Nivolumab as per local practice*

Assessment prior to / during PIPAC treatment cycles

Assessments prior to PIPAC 1

Between the date of randomisation and the date of the first PIPAC all intervention arm participants must attend and be reviewed in a pre-operative assessment clinic (POAC) either at their recruiting site or the corresponding PIPAC/Type B site. Where possible, blood results from screening or from any pre SACT cycle assessments if applicable (colorectal and stomach group participants only) can be used in the POAC and any additional bloods tests will be done at the discretion of the POAC team as per standard practice.

Ovarian group: There is no requirement for participants to have a further set of bloods immediately prior to PIPAC 1 provided all those bloods detailed in Table 8 were done at screening/POAC and the participants clinical picture has not changed. This is because participants in the ovarian arm of the trial are not having systemic chemotherapy. Table 8 All other assessments included in table 8 can be performed at the PIPAC site on the day the participant is admitted for their PIPAC surgery.

Colorectal and stomach groups: participants will attend their recruiting site and have pre op bloods as per Table 8.

- For participants who have SACT in addition to PIPAC in that treatment cycle, bloods must be taken within 72 hours prior to day 1 of the PIPAC treatment cycle. Results of these bloods should be passed onto the surgical team for review who will then advise on the need for any repeat pre-op bloods prior to the PIPAC procedure in that cycle (depending on the day within the cycle that PIPAC has been scheduled).
- For patients who do not have SACT in addition to PIPAC in a PIPAC treatment cycle, bloods should be scheduled within 72 hours prior to the date of the PIPAC procedure (if this is not logistically possible, a window of up to 120 hours prior to PIPAC is permitted).

All other assessments included in table 8 can be performed at the PIPAC site on the day the patient is admitted for their PIPAC surgery

Assessments prior to PIPAC 2 and 3

There is no requirement for participants to attend POAC prior to PIPAC 2 or 3. Instead, these participants will attend their recruiting site and have pre op bloods as per Table 8. All other assessments included in table 8 can be performed at the PIPAC site on the day the participant is admitted for their PIPAC surgery.

Table 8: Assessments required prior to / during each PIPAC treatment cycle

Assessment	Timepoint
Physical assessment (including height (ovarian group PIPAC 1 only), weight)	Colorectal / stomach groups: • Bloods within 72 hours prior to day 1 of PIPAC treatment cycle for participants who have SACT and PIPAC in this treatment cycle • Bloods within 72 hours prior to PIPAC procedure for participants who have PIPAC only in this treatment cycle (if this is not logistically possible a window of up to 120 hours prior to PIPAC is permitted). Ovarian group: • PIPAC cycle 1 - bloods prior to PIPAC 1 for participants do not need to be repeated within 7 days of the PIPAC treatment provided they were done at screening/POAC as these participants will not be having systemic chemotherapy. • PIPAC 2 and 3: bloods should be taken within 7 days prior to the PIPAC procedure. All other assessments can be performed on the day the participant is admitted for their PIPAC surgery.
Vital signs (including blood pressure, heart rate)	
ECOG performance status assessment	
Bloods: FBC, U&Es, Mg^{2+}, LFTs, Cr, bone profile	
Bloods: assessment of tumour marker (CA125 for ovarian patients, CEA for colorectal patients, not applicable to stomach patients)	
ECG *(dependent on pre-op assessment requirements)*	
Urine pregnancy test (WOCBP only)	
AEs / SAEs	Within 72 hours prior to PIPAC
Concomitant medications	Within 72 hours prior to PIPAC
Conversation with PIPAC centre if patient has ascites re: suitability for PIPAC/ if requires tap prior to travel	Minimum of 3 days prior to PIPAC
Documentation of episodes of therapeutic ascitic drainage since randomisation/last treatment cycle. *Ovarian group only*	Within 72 hours prior to PIPAC

If patients do not meet the criteria for undergoing PIPAC procedure, or are receiving treatment with any medicine that may affect the safety of PIPAC (prohibited concomitant medications- see section 11.10), they should not travel to the PIPAC centre and the surgery should be rearranged.

Assessments 30 days after each PIPAC.

30 days after each PIPAC procedure the site RN will call the participant and review their medical notes to collect information on the nature and grade of any surgical complications (Clavien Dindo classification) that have happened in the 30 days since the respective PIPAC procedure. Any AEs/SAEs will also be reported as applicable.

CT scans

CT scans should be performed at the timepoints noted below regardless of delays to SACT and/or PIPAC treatments, but there should always be at least 1 week following a PIPAC procedure to allow time for reduction of post operative inflammation.

Each group should have their scans booked within the following timepoints:

- Colorectal
  - Baseline (should be within 28 days prior to randomisation)
  - 8-10 weeks post-randomisation
  - 19-21 weeks post-randomisation
- Ovarian
  - Baseline (should be within 28 days prior to randomisation)
  - 10-12 weeks post-randomisation
  - 18-20 weeks post-randomisation
- Stomach
  - Baseline (should be within 28 days prior to randomisation)
  - 8-10 weeks post-randomisation
  - 19-21 weeks post randomisation (2 weekly group) or 20-22 weeks post randomisation (3 weekly group)

All groups: 4th and thereafter: every 2 months +/- 2 weeks for the first year after the end of trial treatment, thereafter every 3 months (or as per local SOC) until end of trial. Trial specific CT scans (with RECIST measurements for peritoneal disease reported on the CRFs) will stop at the time of peritoneal disease progression as per RECIST (V1.1).

QoL questionnaires

QoL questionnaires include EORTC QLQ C30 – version 3 and the following EORTC items:

- Fear of recurrence
- Abdominal pain
- Satisfaction with the medical team

These should be completed in line with CT scans, at the following timepoints:

- Colorectal
  - 1st - baseline (after consent, and prior to treatment starting)
  - 2nd - 8-10 weeks post-randomisation
  - 3rd - 19-21 weeks post-randomisation
- Ovarian
  - 1st - baseline (after consent, and prior to treatment starting)

- 2nd - 10-12 weeks post-randomisation
- 3rd - 18-20 weeks post-randomisation

- Stomach
  - 1st - Baseline (after consent, and prior to treatment starting)
  - 2nd - 8-10 weeks post-randomisation
  - 3rd - 19-21 weeks post randomisation (2 weekly group) or 20-22 weeks post randomisation (3 weekly group)

All groups: 4th, 5th and 6th questionnaires:

- 4th - 2 months after CT scan number 3
- 5th - 6 months after CT scan number 3
- 6th - 10 months after CT scan number 3

PIPAC procedure

The dose prescription and management plan will be recorded clearly in the participant's medical records.
Consent for the PIPAC procedure is to be obtained using the standard hospital CF prior to each surgery. Patients should be informed of the following possible risks:

- Risks associated with PIPAC treatment and delivery of intraperitoneal chemotherapy including but not limited to: wound infections and toxicity (see trial PIS for further details)
- Operative risks
- General anaesthetic risks

Table 9 should be followed to assess whether PIPAC can be given to a participant.

Table 9: Requirements to be met prior to PIPAC

Do Not Give PIPAC Unless	Contraindications to PIPAC
• Creatinine clearance ≥50 mls/min. (*Creatinine clearance should be estimated using the online ClinCalc calculator: https://clincalc.com/kinetics/crcl.aspx*) • Serum bilirubin <30 micromol/L • WBC ≥3.0 x 10^9/L • Neutrophils ≥1.5 x 10^9/L • Platelets ≥100 x 10^9/L • No red blood cell fragmentation seen if manual blood film deemed necessary	• Hypersensitive or idiosyncratic reaction to, or any of the components of, the IP chemotherapy product in the past. *(Note a dose reduction of Oxaliplatin is permitted from 120mg/m^2 to 90mg/m^2 due to frailty, intolerance or neuropathy)* • Coagulation disorders and increased bleeding tendency • Prolonged QT interval on ECG • Clinical or radiological evidence of bowel obstruction

PIPAC should be administered as described in the PIPAC Manual provided by the PICCOS trial. Dosing and schedule for intraperitoneal drugs delivery should be as per section 11.1. PIPAC can be delayed if required, as described in section 11.5.

PIPAC is the administration of an aerosolised anti-cancer treatment within the abdominal cavity. The equipment required to do this includes a laparoscopic nebuliser and an injector which together constitute the drug delivery system. There are several CE marked nebulisers and injectors with the required regulatory approval to deliver drugs in this way and only these will be permitted for use during the PICCOS trial.

The PICCOS PIPAC Manual describes the health and safety requirements that must be implemented in theatre. PIPAC has been rigorously tested in numerous international jurisdictions and found to be completely safe if applied responsibly. Safety measures are necessary to comply with health and safety at work laws and regulations. The operating theatre should be equipped with modern ventilation technology satisfying the HTM 03-01 Health Technical Memorandum Specialist Ventilation for Healthcare Premises. This is standard to UK hospitals and the specification will be available from hospital estates department. (72)

PIPAC surgeons will have undergone the ISSPP approved 2-day PIPAC team training course. They will have carried out simulated procedures, dry runs and initial cases will be preceptored by experienced PIPAC surgeons. Standardised and well-tested checklists are utilised throughout the procedure and completeness will be checked at monitoring visits.

Monitoring during surgery

Participants will be closely monitored during the delivery of PIPAC in keeping with standard hospital policy outlining care for patients under general anaesthesia. The Consultant Anaesthetist will monitor the participant remotely by telemetry and all staff will be outside the operating theatre while PIPAC is being delivered with the exception of the treating consultants who may be required to enter theatres if there are problems with PIPAC delivery or if an emergency occurs. All staff members will comply with hospital policy regarding the delivery of chemotherapy.

Post-surgery procedure

Participants will be monitored as per local protocols post abdominal surgery, particularly monitoring the patient for immediate complications such as bleeding and infection. Any signs of toxicity will be documented in the participant's medical notes using CTCAE, reported as AEs/SAEs (as applicable) and the patients' symptoms will be appropriately managed. Surgical complications will also be recorded in medical records and on the CRF using the Clavien-Dindo scale (up to 30 days post each PIPAC procedure).

Guidance for post operative ward staff on caring for patients after PIPAC is included in the PIPAC Manual. At the time of discharge after each PIPAC procedure, the participant should be given a copy of the relevant PICCOS PIPAC discharge information sheet (1a, 1b or 1c).

13.2 Follow-up

All participants will be followed up to the point of peritoneal disease progression as per RECIST (v1.1) or a minimum of six months post-randomisation whichever comes first. Ongoing assessments will end for all patients when the last patient randomised has completed six months of follow up from their randomisation date or for the timeframes specified below. After the end of treatment, participants will have a telephone call from the site RN every 2 months in the first year and then 3 monthly thereafter just prior to each CT scan to review progress and collect follow up data as per Table 10.

Table 10: Follow-up Assessments

Assessment	Timepoint
AEs/ SAEs	For up to 30 days post end of trial treatment only
Documentation of bowel obstruction since last trial visit/follow up phone call (grade CTCAE ≥3 bowel obstruction– record on Toxicity CRF) – *RN from site to call participants to obtain this information prior to each CT scan in the follow up period*	Every 2 months (+/- 2 weeks) for the first year following the 3rd CT scan then every 3 months thereafter or as per local SOC for CT scanning frequency until peritoneal disease progression as per RECIST (v1.1) or end of trial
CT scan (chest, abdomen and pelvis)	Every 2 months (+/- 2 weeks) for the first year following the 3rd CT scan then every 3 months thereafter (or as per local SOC) until peritoneal disease progression as per RECIST (v1.1) or end of trial
Blood test - CA125 for ovarian patients, CEA for colorectal patients, not applicable to stomach patients	Same timepoints as for CT scans until peritoneal disease progression as per RECIST (v1.1) or end of trial
QoL questionnaire	○ 2 months after CT scan number 3 ○ 6 months after CT scan number 3 ○ 10 months after CT scan number 3
Documentation on whether the participant is suitable for curative surgery	Every follow up visit/phone call (every 2 months in the first year of follow up and every 3 months thereafter)
Details of further treatment for colorectal / ovarian or stomach cancer (as applicable) – document type of treatment given and number of lines (courses) of each. *(Information collected by RN at phone call and upon review of medical notes)*	Every 2 months (+/- 2 weeks) in first year after EOT, 3 monthly thereafter until progressive disease as per RECIST (v1.1) or end of trial
Documentation of episodes of therapeutic ascitic drainage since last treatment cycle/last follow up visit. *Ovarian group only*	Every follow up visit/phone call (every 2 months in the first year of follow up and every 3 months thereafter)
Concomitant Medications	For up to 30 days post end of trial treatment only (i.e. same period as AEs/ SAEs)

13.3 Disease response assessment

CT scans should be performed with contrast, and should cover the abdomen, thorax and pelvis as per the timelines described in section 13.1.

Site Radiology Procedure

A PICCOS specific RECIST assessment form has been designed to capture and assess peritoneal metastases. All baseline RECIST assessments should include 2 visible measurable or non-measurable lesions from the peritoneum. If further metastases are seen outside of the peritoneum, these should be captured at the end of the form but do not require formal evaluation. Please mark on the CT scan lesions being assessed / measured (where measurable) for central radiology review.

Central Radiology Procedure

All CT scans performed in the trial will be uploaded to the Cimar platform by site staff prior to central review for the primary endpoint of pPFS.

Access to the Cimar platform will be issued upon this duty being assigned by the PI to site staff on the Site Delegation Log. Scans should be pseudonymised at site prior to upload, leaving only participant trial ID, initials, date of birth (MM, YYYY), male/female and date and time of scan on the scan. Central review will be performed by one member from a Central Review Panel unless there is a discrepancy between the site Radiologist and the Central Reviewers assessment, whereby review by another member of the panel will take place and a consensus opinion obtained.

Central Radiology will repeat/confirm the target lesion measurements/assessment and generate the RECIST calculation.

Disease response will be evaluated for peritoneal and extra-peritoneal disease separately, and overall, as per the primary and secondary endpoints.

Pseudo-Progression

As pseudo-progression is possible within this population, any increases in lesion size (LS) (within the peritoneum) should be confirmed by a second CT scan at the next planned timepoint before any treatment changes occur. Any new lesions should be classed as definite progression and treatment changes may be required.

Assessment of extraperitoneal disease

In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment (SACT/PIPAC) will be made. For participants with ovarian malignancy receiving PIPAC, extraperitoneal progression during treatment will lead to an assessment in regard to the addition of SACT.

14 Pharmacovigilance

The PI is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by a medically qualified Investigator (delegated this duty on site delegation log) at the participating site to the CTR PV and Safety Specialist. This includes SAEs related to IMPs and nIMPs.

SAEs are reportable immediately following informed consent and should be reported until 30 days after the end of trial treatment.

14.1 Definitions

Table 11: SAE definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product

Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an IMP which is related to any dose administered to that participant
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition*** Following a PIPAC procedure, anything that keeps the participant in hospital for ≥48 hours immediately after the procedure should be reported as an SAE.
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

14.2 Trial specific SAE reporting requirements

Events requiring reporting

In addition to the SAE reporting requirements defined in
Table 11, for the purposes of this trial the following events will also be considered SAEs and must be captured on the SAE form and reported to the CTR with 24 hours of knowledge of the event:

- Following a PIPAC procedure, anything that keeps the participant in hospital for ≥48 hours immediately after the procedure should be reported as an SAE.

Events that do not require reporting

For the purposes of this trial the following events will not require reporting as SAEs. These should be completed in the participant's notes and on the relevant toxicities CRF page and forwarded to the CTR in the normal timeframes for CRFs.

- Hospitalisation for PIPAC procedure, only prolonged hospitalisation requires reporting (as per section 14.2).
- Disease progression.
- Death due to disease progression- if this occurs, the death CRF must be completed.

14.3 Causality

Causal relationship will be assessed for IMPs, other trial treatments (nIMPs) and procedures:

Table 12: Colorectal causality

IMPs: mitomycin (IP), oxaliplatin (IP) **nIMPs:** oxaliplatin (IV), sodium folinate (IV), calcium folinate (IV), 5-FU (IV), capecitabine (PO), irinotecan (IV), cetuximab (IV), panitumumab (IV)

Table 13: Ovarian causality

IMPs: cisplatin (IP), doxorubicin (IP), paclitaxel (IV), liposomal doxorubicin (IV) **nIMPs:** none

Table 14: Stomach causality

IMPs: cisplatin (IP), doxorubicin (IP) **nIMPs:** cisplatin (IV), nivolumab (IV), sodium folinate (folinic acid) (IV), calcium folinate (IV), trastuzumab (IV), oxaliplatin (IV), 5FU (IV), capecitabine (PO), pembrolizumab (IV)

The PI (or another delegated medically qualified doctor from the trial team) and CI (or another medically qualified doctor from the TMG) will assess each SAE to determine the causal relationship:

Table 15: SAE relationship

Relationship	Description	Reasonable possibility that the SAE may have been caused by the IMP?
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the	No

Relationship	Description	Reasonable possibility that the SAE may have been caused by the IMP?
	participant's clinical condition, other concomitant treatment).	
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the PI (or delegate) cannot be downgraded by the CI (or delegate), and in the case of disagreement both opinions will be provided.

14.4 Expectedness

The CI (or another delegated appropriately qualified individual) will assess each SAR to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the current to RSI for each IMP. Expectedness decisions must be based purely on whether the event is listed in the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SARs which add significant information on specificity or severity of a known, already documented AE constitute unexpected events. Fatal and life-threatening SARs should not be considered expected (unless explicitly stated in the RSI and approved by the MHRA). For example, an event more specific or more severe than that described in the RSI is considered unexpected.

Reference safety information (RSI) can be found in section 4.8 of the relevant SmPC for IMPs used as per licensed indications (IV IMPs in the control arm of the ovarian group). The RSI for IMPs given via the intraperitoneal route as PIPAC can be found in the PICCOS PIPAC RSI Document. Refer to Table 16 for details.

The RSI for PIPAC has been compiled by the trial team from a review of the PIPAC literature.

Table 16: RSIs for IMPs

IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Paclitaxel (IV)	Paclitaxel 6mg/ml concentrate for solution for infusion Seacross Pharmaceuticals Ltd	Section 4.8

Liposomal doxorubicin (IV)	Doxorubicin pegylated liposomal 2mg/ml concentrate for solution for infusion (Doxorubicin hydrochloride) Accord Healthcare Ltd	Section 4.8
Oxaliplatin (IP as PIPAC)	PICCOS PIPAC Reference Safety Information Document	Whole document
Mitomycin (IP as PIPAC)	PICCOS PIPAC Reference Safety Information Document	Whole document
Cisplatin (IP as PIPAC)	PICCOS PIPAC Reference Safety Information Document	Whole document
Doxorubicin (IP as PIPAC)	PICCOS PIPAC Reference Safety Information Document	Whole document

RSI on any CTR trial will be reviewed regularly according to CTR procedures.

14.5 Reporting procedures

Participating site responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, year of birth and initials. The participant's name or other personal identifiers should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR/pharmaceutical companies may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address: CTR-Safety@Cardiff.ac.uk

SAEs should be reported from the time of randomisation, throughout the treatment period up to, and including 30 days after the participant receives their last dose of trial treatment (IMP / NIMP or PIPAC laparoscopic surgery). SARs (such as long-term side effects of trial treatment under investigation) should continue to be reported until the end of follow-up as defined in the protocol.

SAEs in oncology trials should be graded using the CTCAE v5.0.

An SAE form should contain at least the minimum information:

- Full participant trial number
- An AE/AR

- IMP or trial intervention
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log)

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

All other AEs should be reported on the CRF as described in Section 17.2.

The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until 30 days after the participant receives their last dose of IMP. SARS should continue to be reported until the end of follow-up.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the CI(or their delegate) for an assessment of expectedness.

Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the MHRA and REC.

14.6 SUSAR reporting

Cardiff and Vale University Health Board (C&V) is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (MHRA and REC) as follows:

SUSARs which are fatal or life-threatening must be reported to the MHRA and REC within 7 calendar days of receipt at the CTR.

SUSARs that are not fatal or life-threatening must be reported to the MHRA and REC within 15 days of receipt at the CTR.

If the SUSAR report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report, for all fatal and non-fatal, life threatening and non-life threatening.

Any additional, relevant information must be reported within a further 15 days.

N.B. There is no requirement for the CTR to report SUSARs to nIMPs to the MHRA except in the following instances:

- If the AR is suspected to be linked to an interaction between a nIMP and IMP, and is serious and unexpected, CTR should report as a SUSAR due to the interaction with the IMP
- If a SUSAR is suspected and might be linked to either a nIMP or an IMP and cannot be attributed to only one of these
- If the adverse reaction due to the nIMP is likely to affect the safety of trial participants then CTR should report it to the Sponsor, MHRA and REC in accordance with the relevant SOP for reporting Urgent Safety Measures (USM)

14.7 Safety reports

A list of all SARs (expected and unexpected) will be reported annually to the MHRA, REC and trial sponsor in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA Clinical Trial Authorisation (CTA) approval date.

The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs annually, following submission of the DSUR, throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

14.8 Contraception and pregnancy

Contraception

The IMPs (listed above) in this trial have a demonstrated or suspected human teratogenicity/fetotoxicity. For the purpose of this trial and in line with the Clinical Trial Facilitation Group, women of childbearing potential (WOCBP) will be defined as any woman who is fertile, following menarche and until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophrectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhoea, a single FSH measurement is insufficient. All WOCBP (in accordance with the above definition) entering into this trial must agree to use a highly effective method of contraception preferably with low user dependency for at least six months after the last dose of IMP (or 7 months if treated with the nIMP Trastuzumab (Herceptin)). A highly effective method of contraception is considered as having a failure rate of less than 1%. Some acceptable contraception methods are listed below;

- combined oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable*
- intrauterine device (IUD)*
- intrauterine hormone-releasing system (IUS)*
- bilateral tubal occlusion*
- vasectomised partner*
- sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments.

N.B. periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

**These contraception methods are considered to be low user dependency.*

Male participants with a WOCBP partner should use condom during treatment and at least until six months after the last dose of IMP. For a non-pregnant WOCBP partner, contraception recommendations should also be considered.

Pregnancy reporting whilst participating in the trial

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. Without follow-up of the pregnancy, it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP. Information on a pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form supplied to sites by the CTR.

Sites should report pregnancy occurring within PICCOS SAE reporting periods (30 days following last administration of trial treatment). Congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTR on a trial-specific SAE form. Congenital anomalies or birth defects related to the IMP and unexpected with respect to the IMP RSI must be submitted by the CTR within expedited SUSAR time frames (7 or 15 days) to the MHRA, relevant REC and the drug manufacturer of the IMP (to comply with any contractual agreement).

14.9 Urgent Safety Measures (USMs)

An USM is an action that the Sponsor, CI or PI may carry out in order to protect the participants of a trial against any immediate hazard to their health or safety. Any USMs relating to this trial must be notified to the MHRA and REC immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

15. Statistical considerations

15.1 Randomisation

Site staff who are delegated the role of randomisation will log onto a central web-based platform (see section 9.4), to enter eligible patients into the trial, who will be randomised in a 1:1 ratio to either SOC or PIPAC.

Allocation will be minimised by the PIPAC centre to ensure there is not a disparity in per patient resource costs between sites and balanced on prognostic factors to avoid bias. Within each disease site, the first patient will be allocated at random, and then minimisation with a 20% random element will be used to allocate the next participant to the treatment which reduces the overall imbalance across all prognostic factors.

15.2 Sample Size

In each of our three disease areas we are using a randomised phase II screening design to detect whether PIPAC shows enough activity to warrant further assessment in confirmatory phase III trials. The 1:1 randomisation allows PIPAC (with or without SACT) to be compared to a concurrent control group who will receive SACT. Each trial is powered to detect a Hazard Ratio (HR) of 0.55, as we will need to see a large effect size at this phase II stage to warrant further investigation. Using a high power of 90% means that we have a high chance of detecting a true improvement in PFS, but since confirmatory trials would be required, a 20% probability of a false positive is acceptable in this setting. A one-sided test is also employed because we only need to demonstrate an improvement in our primary outcome at this stage. In each disease setting, we have assumed that the published median PFS estimates will be a suitable estimate for the peritoneal-specific PFS, since PM will be selected as target lesions in all patients, and we are confident that PM are the driver of progression events in our target population. The artmenu package in Stata 17 was used to calculate the sample size.

Colorectal

In an individual patient data (IPD) meta-analysis of 1,375 colorectal patients with PM, PFS was estimated to be 6 months with standard care(5). There is no randomised data on the effect of PIPAC on PFS or OS in colorectal cancer patients. To demonstrate that PIPAC has enough activity in this group to warrant further phase III investigation, we need to show improvement in median PFS to 11 months (HR 0.55, 20% one-sided significance, 90% power). This requires 51 PFS events and 66 patients recruited over 2.5 years, with an additional 6-month follow-up at the end of recruitment. This is inflated to 78 to allow for early dropouts due to not being fit for PIPAC.

Ovarian

Median PFS is estimated at 3.4 months with standard care(7). There is no randomised data on the expected PFS in the PIPAC group. To demonstrate PIPAC has activity in this group we need to show an improvement in PFS to 6 months (HR 0.55 20% one-sided significance, 90% power). This requires 52 events and 58 patients recruited over 2.5 years, with an additional 6-month follow-up at the end of recruitment. This is inflated to 66 to allow for early dropouts due to not being fit for PIPAC.

Stomach

PFS is estimated at 5 months in the SOC arm, which is close to that assumed by the French PIPAC phase II trial in stomach cancer(95). To demonstrate PIPAC has activity in this group we need to show an improvement in PFS to 9 months (HR 0.55, 20% one-sided significance, 90% power). This requires 52 events in 63 patients, recruited over 2.5 years, with an additional 6-month follow-up at the end of recruitment. This is inflated to 72 to allow for early dropouts due to not being fit for PIPAC.

15.3 Missing, unused & spurious data

If a patient is missing RECIST data for the primary endpoint (peritoneal PFS), due the RECIST assessment being unavailable or unevaluable, then participants will be censored at the date of their last evaluable RECIST assessment, unless they die prior to missing their second follow-up RECIST assessment, in which case the date of death will be used. If a patient has no evaluable RECIST assessment and have not died prior to their 2nd follow-up RECIST assessment, they will be censored at day 1.

Missing data from the QLQ-C30 will be treated as follows, if at least half of the items from a multi-item scale are missing, assume the missing items have an average value of the items that are present, for cases where more than half of an item scale is missing, or a single arm is missing these will remain as missing.

Full details for handling missing or unevaluable data for primary and secondary endpoints will be provided in the Statistical Analysis Plan (SAP).

15.4 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

15.5 Termination of the trial

We will evaluate feasibility of randomisation using the hypothesis testing traffic light method (96), alongside stipulating minimum numbers to be recruited by 18 months into the trial. In the first 85 eligible patients invited for randomisation within each cancer type, if ≥30% patients are randomised, we will continue to recruit to the required sample sizes, if <15% are randomised, we will declare recruitment is not feasible, if randomisation is between 15-30%, we will continue but consider any adaptions we could make to improve recruitment. Using this method requires at least 13 of the first 85 invited participants to consent to randomisation in each disease site. This will include speaking to sites as to why recruitment is barrier and reviewing the following: the way patients are approached and invited to the trial; the participant information sheet; eligibility criteria. We would also consider the option of stepping up the publicity surrounding the trial. Throughout the trial we will make every effort to ensure sites have access to the PICCOS team and are receiving the right support.

15.6 Inclusion of analysis

We will include all randomised participants in the analysis of peritoneal progression free survival and overall progression free survival on an intention to treat basis, censoring patients with no evaluable RECIST assessments at day 1. Patients with no PFS events will be censored at the date of their last CT scan if the RECIST assessment is evaluable. All participants will be included in the overall survival analysis, patients with no death events will be censored at the date last reported to be alive by the site.

The feasibility population consists of all randomised patients who are potentially eligible and are given the PIS and invited to take part in the PICCOS trial.

A per-protocol analysis population will exclude participants who do not receive any chemotherapy, and PIPAC patients who do not receive PIPAC. The per protocol analysis will also exclude participants who have a protocol violation affecting analysis.

The safety dataset will include all participants who received any chemotherapy or PIPAC as part of the trial.

16 Analysis

16.1 Main analysis

The feasibility of randomisation will be assessed by a tabulation of the number of potentially eligible patients invited to take part and given the PIS, and the number of those who give their consent to be randomised. This will be broken down by the first 85 patients approached and overall. The reasons for declining to consent to randomisation will also be included in the tabulation.

Analysis of primary and secondary endpoints will be performed for each disease area separately, and since this is a phase II trial, there will be no adjustment to account for multiplicity of testing. Analysis will be performed on an intention to treat basis, when the required number of peritoneal PFS events (from the sample size) have been recorded in each disease and following a minimum 6-month follow-

up. PFS date will be derived from CT scan dates, not visit dates. The primary analysis will be based on the results of a centralised review of CT scans.

Patients who have not progressed in the peritoneum or died at the time of analysis will be censored at the time of the latest evaluable RECIST assessment. Patients who progress or die after missing at least two RECIST assessments will be censored at the last RECIST assessment. Patients with no RECIST assessments evaluable for peritoneal disease will be censored at day 1 unless they die within two RECIST visits of baseline (colorectal = 21 weeks, ovarian = 20 weeks, stomach = 22 weeks). Peritoneal PFS will be estimated using the Kaplan–Meier method and will be described in terms of median PFS per arm. The log-rank test, stratified by prognostic factors, will be used to compare progression-free survival distributions in the two trial arms. A one-sided p-value will be calculated, if this is less than 0.2 and the outcome favours the PICCOS treatment group, then we will consider there to be sufficient statistical evidence of activity in the PICCOS arm to warrant further investigation. We will use multivariable Cox regression to estimate the adjusted HR and one-sided 80% upper confidence interval, adjusted for key prognostic factors such as PCI (if the proportional hazards assumption is not violated). If there is evidence of non-proportional hazards, then we will calculate the restricted mean survival times in each group.

Cox regression will be used to estimate the HR and associated 95% confidence intervals for the secondary time-to-event endpoints of overall PFS and overall survival, but no formal log-rank tests will be performed for these. Overall PFS (peritoneal and extra-peritoneal disease combined) will consider any evidence of disease progression from both peritoneal and extra-peritoneal lesions.

The peritoneal specific overall response rate and the peritoneal specific disease control rate will be calculated for each group with 95% confidence intervals.

The mean difference in global health scores between groups will be summarised at the end of treatment QoL timepoint. The median global health scores from the QLQ-c30 will be calculated with the inter-quartile range (IQR) at each QoL time point and summarised graphically with boxplots over time for each group. The following functional scales will also be summarised as for global health score above, physical functioning, role functioning and emotional functioning. Single symptom items of pain, fatigue, fear of recurrence, abdominal pain and satisfaction with the medical team will be summarised as above.

The worst grade reported at any point during the trial of any treatment toxicity, or surgical complications affecting at least 5% of participants will be tabulated by grade for each arm. The overall number of episodes of neutropenic sepsis and bowel obstruction will also be summarised.

The outcome of PIPAC procedure will also be summarised, including the number of patients with one, two or three successful procedures, the number of cases of failed abdominal entry, and the number of participants with stomach or colorectal tumours who become eligible for curative surgery following PIPAC. The reasons for failure of procedure will be summarised.

The full plan for analysis will be detailed in the SAP. We plan to share data from the PICCOS trial to evaluate PIPAC in meta-analysis for each disease setting.

16.2 Sub-group & interim analysis

No formal subgroup analysis is planned. Interim analysis will be performed to assess the feasibility outcomes as described above.

17 Data Management

Source Data is defined as "All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents." There is only one set of source data at any time for any data element, as defined in site source data agreement.

17.1 Data collection

Patient randomisation and data collection will take place via electronic online database.

17.2 Completion of CRFs

Data recording for this trial will be via web-based systems. These are secure encrypted systems which comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018 standards. After a site has supplied the CTR trial team with a completed delegation log and completed all other processes required to open for recruitment, each user at the site will be emailed a link to activate their account and a username by which they can access these systems in combination with a password set by the user.

The randomisation system and data entry systems can be accessed via: https://redcap.ctr.cardiff.ac.uk/redcap/

Sites will be provided with a guide on using these systems.

Data is expected to be entered by sites within four weeks after the scheduled visit/assessment. If a participant misses a visit/assessment but relevant data is available, for example from a hospital visit unrelated to the trial, this data should be provided. Data queries will be flagged on RedCAP by the CTR trial team; unresolved queries and overdue forms will be flagged via email to the site on a regular basis.

Participants who are seen at a "PIPAC site" that is different to their "Recruiting site" will have data entered on their CRF by staff at the "Recruiting site" and the "PIPAC site" as applicable to the relevant activities that are undertaken at the respective sites and as delegated to individual staff members on the "Recruiting site's" PICCOS Delegation Log by the Recruiting site PI.

17.3 Quality of Life questionnaires

Completed paper quality of life questionnaires containing the participant's trial ID, month and year of birth, initials and date of completion:

- if completed by the participant at site, data from the questionnaire should be entered into REDCap by site staff. The questionnaire should then be kept in the participant site file at site.
- If a completed by the participant at home, the questionnaire it can either be returned by the participant to site for data entry at their next scheduled visit or can be returned to the CTR using the Freepost labels contained within the Investigator Site File (ISF) and 'Confidential' marked on the envelope. CTR will then scan and securely email the questionnaire to the site for data entry into REDCap.

18 Translational research

Details of planned future translational research will be added in a substantial amendment once funding has been secured.

19 Qualitative Sub-study

Aims and objectives

Qualitative research methods provide an opportunity to elicit and characterise patients' experiences of their disease and treatment (97,98), as well as capturing health professionals' experiences of patient care and management (99). The Bristol Biomedical Research Centre (BRC) Surgical and Orthopaedic Innovation theme have established research methods to understand patient experiences of new procedures and/or devices as they are being developed, evaluated, and introduced into clinical practice and to understand how the procedure itself develops(100). These will be embedded into the PICCOS trial to meet the sub-study objectives:

i. Explore stakeholder perspectives and experiences of PIPAC treatment, including its impact on symptoms and QoL.
ii. Investigate if there are QoL issues that are unique to patients with PM, including those undergoing PIPAC treatment and standard care.

Methods

One-to-one, semi structured interviews will be conducted to explore views and experiences of PM and PIPAC treatment. We will investigate if there appear to be any unique QoL issues experienced by patients with PM, including those undergoing and following PIPAC treatment and standard care, that may be required to supplement the core set of outcomes for PM disease (70), and if so, determine what these are.

Patients and healthcare professionals will be asked to consent to taking part in the sub-study. All potential participants will be provided with a relevant PIS, given the opportunity to ask questions about the qualitative sub-study and informed, through discussions and sub-study materials, that participation in the sub-study is voluntary and does not affect their participation in the main trial. Healthcare professionals with experience of delivering and caring for patients during and after PIPAC treatment will be identified and approached directly by the qualitative research team. Additional interviewees will be identified by the snowball technique, in which healthcare professionals provide the names of other colleagues who could be interviewed. Healthcare professionals may be invited to take part in multiple interviews as their experience of PIPAC develops. Eligible patients will be identified by the clinical team. Patients who are willing to be contacted for an interview will have their details sent securely by email to the qualitative team research via CTR to allow contact. Participants will be purposively sampled to include a range of healthcare professionals (clinical specialty, experience of PIPAC and roles in patient care) and patients receiving PIPAC treatment or SOC (in the colorectal, ovarian and stomach groups).

Interviews will be undertaken by phone, in person or on-line (depending on participant preference and logistical/practical circumstances) and conducted by a qualitative researcher. Interviews will last approximately 30-45 minutes and will be arranged at a time and date convenient for the participant. Separate topic guides will be developed for healthcare professionals and patients, to ensure that discussions within each group cover the same basic issues but with sufficient flexibility to allow new issues of importance to the informants to emerge. Patients will be interviewed over a range of timepoints (maximum of two) to understand if experiences differ over time and recovery.

Interviews will be digitally recorded on encrypted audio-recording devices. These data will be transcribed and imported into qualitative software for analysis (e.g. Nvivo). Transcripts will be analysed thematically using constant comparison techniques (101). Data collection and analysis will proceed in parallel, with emerging findings informing further sampling (theoretical sampling) and data collection. Data collection will ultimately continue until additional data are not adding anything new to the analytical framework and theoretical saturation is felt to have been achieved. Comparisons will be made between the interview data (reported QoL issues) and the published literature (issues that are reported in colon, ovarian and stomach patients and are generic aspects of QoL (e.g. fatigue) or clinical outcomes (e.g. survival), to identify the presence of any PM or PIPAC specific issues.

Findings will inform the need to identify existing validated patient-reported outcome measures, or develop a new measure, to address the relevant QoL issues and optimal design of the future Phase III trial.

Data management

Upon initial consent to the sub-study, participants will be given a unique identifying (ID) number. All subsequent data collected for the sub-study will be labelled by this ID number and data will not include any identifiable information. The sub-study ID number will be linked to personal information (e.g. names and contact details) in a key breaker document which will be encrypted, password protected and stored securely on the University of Bristol servers.

Digital audio files, recorded using encrypted audio-recorders (supplied by the University of Bristol), will be transferred securely to and retained by the University of Bristol. Transfer will be performed using an encrypted electronic data transfer system to ensure safe and secure transfer of digital data. All digital data will be stored securely on the University of Bristol servers, adhering to university data storage policies.

Audio files will be transcribed by an approved, professional transcriber who holds a contract with Cardiff University. Transcripts will be de-identified (i.e. will not include any personal information) to mitigate the risk that participants are identified. Only authorised members of the research team will have access to the audio recordings and transcripts. The transcripts and the audio recordings will be stored in separate locations on University of Bristol servers. The transcript data may be used as part of publications, teaching and presentations at meetings. All quotes will be pseudonymised so that participants cannot be identified. Information about how the data are stored and used is provided in the information sheets for patients and healthcare professionals, and individuals will be asked to confirm they understand how their data will be used as part of the consent process.

20 Protocol/GCP non-compliance

The PI should report any non-compliance to the trial protocol or the conditions and principles of GCP to the CTR in writing (on the Non-compliance Site Proforma, emailed to PICCOS@cardiff.ac.uk) as soon as they become aware of it.

21 End of trial definition

The treatment phase will be followed by a non-interventional follow-up period which will continue for at least 6 months after the last participant is randomised.

The end of the trial is defined as the date of final data capture to meet the trial endpoints. In this case end of trial is defined as the final follow-up collection, which will be at least 6 months after final patient is randomised.

Sponsor must notify the MHRA and REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

22 Archiving

The Trial Master File (TMF) and Trial Statistical File (TSF) containing essential documents will be archived at an approved external storage facility for a minimum of 15 years after completion of the trial. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The PI is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

The TMF and ISF containing essential documents will be kept for a minimum of 25 years after completion of trial. Documents (paper and electronic) will be retained in a secure location during and after the trial has finished.

A label stating the required retention time should be placed on the inside front cover of the medical records for trial participants. Each PI at any participating site will archive the essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement.

Essential documents pertaining to the trial shall not be destroyed without permission from the sponsor.

23 Regulatory considerations

23.1 CE Mark

PIPAC is the administration of an aerosolised anti-cancer treatment within the abdominal cavity. The equipment required to do this includes a laparoscopic nebuliser and an injector which together constitute the drug delivery system. There are several CE marked nebulisers and injectors with the required regulatory approval to deliver drugs in this way and only these will be permitted for use during the PICCOS trial.

23.2 CTA

This trial has CTA from the UK Competent Authority: MHRA.

23.3 Ethical and governance approval

This protocol has a favourable opinion from a REC that is legally "recognised" by the UK Ethics Committee Authority for review and approval.

This trial protocol will be submitted through the relevant permission system for global governance review dependant on the location of the lead site.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. Confirmation of C&C of the host care organisation must be obtained before recruitment of participants within that host care organisation.

23.4 Amendments

The CI will seek advice from C&V R&D office prior to submission of amendments to the relevant bodies. The CI will seek approval for any substantial amendments to the protocol or other trial documents from HRA/HCRW and MHRA/REC (if applicable). The NHS R&D Office(s) will need to confirm C&C prior to implementation. Amendments to the protocol or other trial documents will not be implemented prior to these approvals being granted. Non-substantial amendments should be notified to the HRA/HCRW and REC for information and may also need to be reviewed and accepted by R&D departments before they can be implemented in practice at site(s).

Any major amendments to this protocol will be approved by the MHRA, REC and HCRW. Minor amendments may only be approved by REC and HCRW.

23.5 Data protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the UK GDPR and Data Protection Act 2018. Participants will be identified using their unique trial identification number and data will be stored alongside the participants initials and full date of birth.

Participants NHS numbers will be securely stored:

- at the Sponsor organisation to facilitate the logistical organisation of PIPAC surgical procedures.
- at the CTR separate to the main trial data to allow long term monitoring of health status.

The data custodian and the translational sample custodian for this trial is C&V.

23.6 Indemnity

This is an NHS-sponsored research trial, and the NHS indemnity scheme therefore applies. If there is negligent harm during the trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. The NHS indemnity scheme does not cover non-negligent harm.

Claims from participants for harm arising from their participation in the clinical trial will be managed in accordance with standard NHS claims procedures for which NHS indemnity schemes will apply.

Cardiff University has insurance in place (Clinical Trial and Professional indemnity) to cover the CTR staff working on the trial.

23.7 Trial sponsorship

The sponsor of this trial is C&V. It is the role of the sponsor to confirm that there are proper arrangements to initiate, manage, monitor, and finance a trial. The sponsor will not play a role in the trial design, conduct, data analysis and interpretation, manuscript writing, or the dissemination of results; this will be the responsibility of the CI, CTR trial team and TMG, either as an employee of the sponsor organisation or with a delegated responsibility.

The sponsor has responsibility for overall oversight of the trial. The role of the Sponsor is to ensure the trial is run safely and effectively by requiring the following:

- Proportionate peer review.
- Provision of all appropriate, valid supporting documentation at the point of application.
- Clear definition of roles and responsibilities of organisations and individuals, signed off prior to the trial commencing.
- Appropriate level of monitoring and audit.
- A risk assessment process to identify any potential risks to the organisation or the health, safety, and well-being of researchers and research participants.
- Involvement of patients and/or the public in trial design, where appropriate.
- The CIs suitability to fulfil their role, through relevant experience and appropriate training.
- Dissemination of trial findings in an appropriate manner.

The Sponsor, through their R&D department, has a veto on overall approval for the trial.

The funder's role is to finance the trial and to receive a trial report. The trial is being sponsored by C&V with responsibilities delegated to participating centres as per the site agreements.

Sponsor has also delegated responsibilities to the CTR as per the agreements. CTR will also ensure that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments
- Conditions and principles of GCP
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research
- UK GDPR and Data Protection Act 2018
- The Human Tissue Act 2004
- Other regulatory requirements as appropriate
- NIHR Terms and Conditions

23.8 Funding

The PICCOS trial has been funded by the NIHR EME. Funder reference NIHR151274.

23.9 Participant payments

Due to the travel required by participants receiving PIPAC within the PICCOS trial, they will be eligible for reimbursement. This will be up to £45 per participant, per PIPAC. This is calculated as an average of 100 miles round trip paid at the standard NIHR mileage rate of 45p/mile. Sites may use some discretion as long as the average across participants does not exceed this amount.

24 Trial management

The sponsor is responsible for uploading the end of trial summary results to EudraCT as per the commission's guidelines on posting and publication of result-related information.

24.1 Trial Management Group

The PICCOS TMG will consist of CTR members, surgical and oncology leads from each disease group, research fellows and patient representatives for each disease group. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

The TMG will meet at least every 3 months. The TMG will monitor progress of the trial including recruitment and retention rates, screening logs, safety reporting and other items which may vary depending on the timepoint of the trial. The TMG will also review any data or sample requests received by the PICCOS trial.

A Patient Advisory Group (PAG) will discuss patient relevant issues and outcomes of these discussions will be fed back to the TMG.

Additional safety reviews will be performed from the point that the first participant taking Nivolumab in the stomach group intervention arm has their first PIPAC to the last date of the pharmacovigilance reporting period for the first 4 participants who have Nivolumab and PIPAC. The toxicity profiles (AEs and SAEs) will be reviewed for these 4 participants within the TMG meetings.

24.2 Trial Steering Committee

TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter. The TSC will meet at least annually and will monitor and review key elements of trial progress including recruitment, Independent Data Monitoring Committee (IDMC) recommendations, and overall management of the trial.

24.3 Independent Data Monitoring Committee

IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter. The IDMC will meet at least annually and will review recruitment, safety and efficacy of the PICCOS trial and provide recommendations to the TSC and TMG.

25 Quality Control and Assurance

25.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the PICCOS trial. Moderate monitoring levels will be employed and are fully documented in the trial monitoring plan. An appropriately trained PIPAC surgeon will monitor the first PIPAC case at each site to ensure they are being performed as per ISSPP training.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

25.2 Central review of radiology

All CT scans performed in the trial will be uploaded to the Cimar platform by site staff prior to central review for the primary endpoint of pPFS.

Access to the Cimar platform will be issued upon this duty being assigned by the PI to site staff on the Site Delegation Log. Scans should be pseudonymised at site prior to upload, leaving only participant trial ID, initials, date of birth (MM, YYYY), male/female and date and time of scan present. Central review will be performed by one member from a Central Review Panel unless there is a discrepancy between the site Radiologist and the Central Reviewers assessment, whereby review by another member of the panel will take place and a consensus opinion obtained.

25.3 Audits & inspections

The trial may be subject to inspection and audit by C&V R&D office under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research 2017.

Direct access will be granted to authorised representatives from the sponsor and host institution for monitoring and/or audit of the trial to ensure compliance with the relevant data protection legislation.

The trial is participant to inspection by the MHRA as the regulatory body. The trial may also be participant to inspection and audit by C&V under their remit as Sponsor.

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data / documents.

The site must inform the CTR of any MHRA inspections.

26 Publication policy

All publications and presentations relating to the trial will be authorised by the TMG.

27 Milestones

Recruitment will last ~2.5 years in PICCOS. The last patient will be followed up for 6 months after their randomisation date. Analysis / close down will last a further 6 months.

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29 Appendices

29.1 PCI

The PCI quantitatively combines the distribution of tumour throughout 13 abdominopelvic regions with a LS score.

Two transverse and two sagittal planes divide the abdomen into 9 regions (Figure 5). The upper transverse plane is located at the lowest aspect of the costal margin, and the lower transverse plane is placed at the anterior superior iliac spine. The sagittal planes divide the abdomen into three equal sectors. The lines define 9 regions, which are numbered in a clockwise direction with 0 at the umbilicus and 1 defining the space beneath the right hemidiaphragm. Regions 9 through 12 divide the small bowel into upper and lower jejunum and upper and lower ileum. To make the PCI tool more quantitative and reproducible, each region is not only defined by the surface landmarks as previously described but can also be defined by the anatomic structures found in each region (table 20).

LS score refers to the greatest diameter of tumour implants that are distributed on the peritoneal surfaces. LS-0 indicates no implants seen. LS-1 indicates implants less than 0.25 cm. LS-2 indicates implants between 0.25 and 2.5 cm. LS-3 indicates implants greater than 2.5 cm. It refers to the greatest diameter of tumour implants that are distributed on the peritoneal surfaces. Primary tumours or localized recurrences at the primary site that can be removed definitively are excluded from the assessment. If there is confluence of disease matting abdominal or pelvic structures together, this is automatically scored as L-3 even if it is a thin confluence of cancerous implants. The LS are then summated for all abdominopelvic regions.

The extent of the disease within all regions of the abdomen and pelvis is indicated by a numerical score from 0 to 39.

Figure 5: PCI

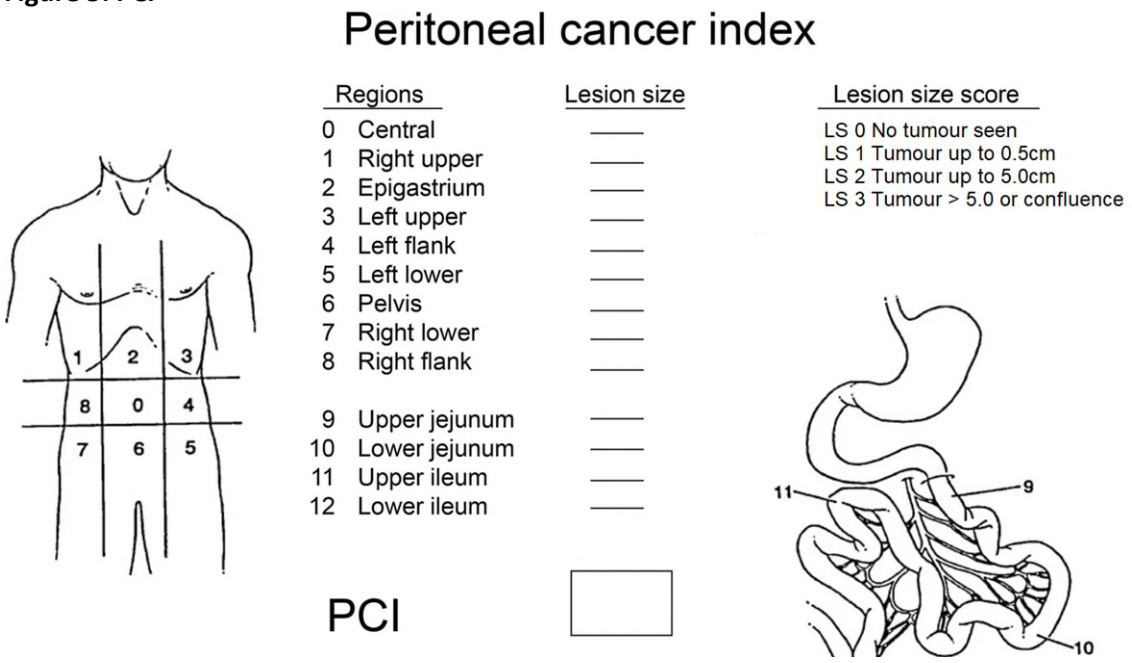


Table 17: Anatomic structures involved in the 13 abdominopelvic regions of the PCI

Regions	Anatomic structures
0 Central	Midline abdominal incision – entire greater omentum – transverse colon
1 Right upper	Superior surface of the right lobe of the liver – undersurface of the right hemidiaphragm – right retro hepatic space
2 Epigastrium	Epigastric fat pad – left lobe of the liver – lesser omentum – falciform ligament
3 Left upper	Under surface of the left hemidiaphragm – spleen – tail of pancreas – anterior and posterior surfaces of the stomach
4 Left flank	Descending colon – left abdominal gutter
5 Left lower	Pelvic sidewall lateral to the sigmoid colon – sigmoid colon
6 Pelvis	Female internal genitalia with ovaries, tubes and uterus – bladder, Douglas pouch – rectosigmoid colon
7 Right lower	Right pelvic sidewall – caecum – appendix
8 Right flank	Right abdominal gutter – ascending colon
9 Upper jejunum	
10 Lower jejunum	
11 Upper ileum	
12 Lower ileum	

29.2 ECOG

Table 18: ECOG Criteria

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Dead

29.3 RECIST V1.1

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.

29.4 Schedule of assessments

Table 19: Colorectal group control arm schedule

Activity	Screening	Randomisation	Each treatment cycle	8-10 weeks post rand	19-21 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
Informed consent	X											
Randomisation		X										
Medical history, pt demographics/ethnicity	X											
Height and weight[1]			X									
Vital signs and physical assessment	X		X									
ECOG	X		X									
Blood test - FBC, U+Es, LFTs, bone profile	X		X									
Blood test - magnesium			X									
Blood test - CEA[3]		X (baseline)	X			X	X	X	X	X	X	X
Blood test - DPYD[2]	X											
Urine pregnancy test WOCBP	X											
MMR/MSI testing on tumour biopsy[2]	X											
CT scan and upload to CIMAR[4]	X			X	X	X	X	X	X	X	X	X
QoL questionnaire completion[5]		X (baseline)		X	X	X		X		X		
Administer SACT[6]			X									
Record concomitant medications	X		X									
Report AEs / SAEs[7]			X	X	X	X	X	X	X	X	X	X
CRF completion	X	X	X	X	X	X	X	X	X	X	X	X

1 Height to be measured prior to cycle 1 only, weight to be measured prior to all treatment cycles.
2 MMR/MSI testing of tumour biopsy and DPYD blood test can take place any time prior to randomisation.
3 CEA blood test to be performed at baseline, pre each treatment cycle and then at the same timepoints as CT scans in follow up until peritoneal disease progression as per RECIST (v1.1) or end of trial.
4 CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform. CT scans should be performed prior to trial entry and then 8-10 weeks and 19-21 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment will be made.
5 QoL questionnaires to be completed alongside CT scans, at baseline, 8-10 weeks post randomisation, 19-21 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.
6 SACT is to be administered according to the protocol. Participants who show extraperitoneal disease progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.
7 AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of CTCAE grade $\geq$3 bowel obstruction.

Table 20: Colorectal group intervention arm schedule

Activity	Screening	Randomisation	PIPAC treatment cycles			Each non PIPAC cycle	8-10 weeks post rand	19-21 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
			Pre op	Each PIPAC cycle	30 days post PIPAC										
Informed consent	X														
Surgeon – participant consulation[1]			X												
RN – participant phone call[2]			X												
Randomisation		X													
Medical history, pt demographics / ethnicity	X														
Height and weight[3]			X			X									
Vital signs and physical assessment	X		X			X									
ECOG	X		X			X									
Blood test - FBC, U+Es, LFTs, bone profile	X		X[7]			X									
Blood test - magnesium			X[7]			X									
Blood test - CEA[5]		X (baseline)	X[7]			X			X	X	X	X	X	X	X
Blood test - DPYD[4]	X														
Urine pregnancy test - WOCBP	X		X												
MMR/MSI testing of tumour biopsy[4]	X														
ECG[8]			X												
CT scan and upload to CIMAR[9]	X						X	X	X	X	X	X	X	X	X
QoL questionnaire completion[10]		X (baseline)					X	X	X		X		X		
POAC[6]			X												
PIPAC procedure				X											
Administer SACT[11]				X		X									

Activity	Screening	Randomisation	PIPAC treatment cycles			Each non PIPAC cycle	8-10 weeks post rand	19-21 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
			Pre op	Each PIPAC cycle	30 days post PIPAC										
Record concomitant medications	X		X			X									
Report AEs / SAEs[12]			X	X	X	X	X	X	X	X	X	X	X	X	X
Clavien Dindo classification[13]					X										
PCI scoring[14]				X											
CRF completion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Optional consultation (either in person or virtual) between the PIPAC surgeon and the participant can take place between date of randomisation and date of PIPAC 1 to discuss the participant's upcoming PIPAC procedure.

2 PICCOS RN will call participant approximately 24 hours prior to each PIPAC to ensure the participant is ready for their procedure.

3 Height to be measured prior to cycle 1 only, weight to be measured prior to all treatment cycles.

4 MMR/MSI testing of tumour biopsy and DPYD blood test can take place any time prior to randomisation.

5 CEA blood test to be performed at baseline, pre each treatment cycle and then at the same timepoints as CT scans in follow up until peritoneal disease progression as per RECIST (v1.1) or end of trial.

6 Between the date of randomisation and the date of the first PIPAC all participants must attend and be reviewed in a POAC either at their recruiting site or the corresponding PIPAC/Type B site. Where possible, blood results from screening or from any pre SACT cycle assessments can be used in the POAC and any additional bloods tests will be done at the discretion of the POAC team as per standard practice. There is no requirement for participants to attend POAC prior to PIPAC 2 or 3.

7 Bloods within 72 hours prior to day 1 of PIPAC treatment cycle. Results of these bloods should be passed onto the surgical team for review who will then advise on the need for any repeat pre-op bloods prior to the PIPAC procedure in that cycle (depending on the day within the cycle that PIPAC has been scheduled).

8 ECG required only if indicated by pre-op assessments.

9 CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform. CT scans should be performed prior to trial entry, 8-10 weeks and 19-21 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment (SACT/PIPAC) will be made.

10 QoL questionnaires to be completed alongside CT scans, at baseline, 8-10 weeks post randomisation, 19-21 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.

11 SACT is to be administered according to the protocol. Note in PIPAC cycles the only permitted SACT are capecitabine, 5FU infusion (not bolus), cetuximab and panitumumab (as applicable). Washout periods included in the protocol should be observed. Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.

12 AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of CTCAE grade ≥3 bowel obstruction.

13 Approximately 30 days after each PIPAC, a RN will call the participant, review their medical notes since their last PIPAC and document the appropriate Clavien Dindo classification(s) for this time period and report AEs/SAEs as required.

14 PCI scoring is to be performed by the surgeon during laparoscopic surgery for PIPAC.

Table 21: Ovarian group control arm schedule

Activity	Screening	Randomisation	Each treatment cycle	10-12 weeks post rand	18-20 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
Informed Consent	X											
Randomisation		X										
Medical history, pt demographics/ethnicity	X											
Height and weight[1]			X									
Vital signs and physical assessment	X		X									
ECOG	X		X									
Blood test - FBC, U+Es, LFTs, bone profile	X		X									
Blood test - magnesium			X									
Blood test - CA125[2]		X (baseline)	X			X	X	X	X	X	X	X
CT scan and upload to CIMAR[3]	X			X	X	X	X	X	X	X	X	X
QoL questionnaire completion[4]		X (baseline)		X	X	X		X		X		
Administer SACT as per protocool[5]			X									
Record concomitant medications	X		X									
Report AEs / SAEs[6]			X	X	X	X	X	X	X	X	X	X
CRF completion	X	X	X	X	X	X	X	X	X	X	X	X

1 Height to be measured prior to cycle 1 only, weight to be measured prior to all treatment cycles.

2 CA125 blood tests to be performed at baseline, pre each treatment cycle and then at the same timepoints as CT scans in follow up until peritoneal disease progression as per RECIST (v1.1) or end of trial.

3 CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform. CT scans should be performed prior to trial entry, 10-12 weeks and 18-20 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment will be made.

4 QoL questionnaires to be completed alongside CT scans, at baseline, 10-12 weeks post randomisation, 18-20 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.

5 SACT is to be administered according to the protocol. Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.

6 AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of CTCAE grade ≥3 bowel obstruction.

Table 22: Ovarian group intervention arm schedule

Activity	Screening	Randomisation	Each PIPAC treatment cycle			(Each non PIPAC treatment cycle)	10-12 weeks post rand	18-20 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
			Pre op	PIPAC treatment cycle	30 days post PIPAC										
Informed Consent	X														
Surgeon – participant consulation[1]			X												
RN – participant phone call[2]			X												
Randomisation		X													
Medical history, pt demographics/ethnicity	X														
Height and weight[3]			X			(X)									
Vital signs and physical assessment	X		X			(X)									
ECOG	X		X			(X)									
Blood test - FBC, U+Es, LFTs, bone profile	X		X[6]			(X)									
Blood test - magnesium			X[6]			(X)									
Blood test - CA125[4]		X (baseline)	X[6]			(X)			X	X	X	X	X	X	X
ECG[7]			X												
CT scan and upload to CIMAR[8]	X						X	X	X	X	X	X	X	X	X
QoL questionnaire completion[9]		X (baseline)					X	X	X		X		X		
POAC[5]			X												
PIPAC procedure				X											
Administer SACT [10]						(X)									
Record concomitant medications	X		X			(X)									
Report AEs / SAEs[11]			X	X	X	(X)	X	X	X	X	X	X	X	X	X

Activity	Screening	Randomisation	Each PIPAC treatment cycle			(Each non PIPAC treatment cycle)	10-12 weeks post rand	18-20 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
			Pre op	PIPAC treatment cycle	30 days post PIPAC										
Clavien Dindo classification[12]					X										
PCI scoring[13]				X											
CRF completion	X	X	X	X	X	(X)	X	X	X	X	X	X	X	X	X

1 Optional consultation (either in person or virtual) between the PIPAC surgeon and the participant can take place between date of randomisation and date of PIPAC 1 to discuss the participant's upcoming PIPAC procedure.

2 PICCOS RN will call participant approximately 24 hours prior to each PIPAC to ensure the participant is ready for their procedure.

3 Height to be measured prior to cycle 1 only, weight to be measured prior to all treatment cycles.

4 CA125 blood test to be performed at baseline, pre each treatment cycle and then at the same timepoints as CT scans in follow up until peritoneal disease progression as per RECIST (v1.1) or end of trial.

5 Between the date of randomisation and the date of the first PIPAC all participants must attend and be reviewed in a POAC either at their recruiting site or the corresponding PIPAC/Type B site. Where possible, blood results from screening can be used in the POAC and any additional bloods tests will be done at the discretion of the POAC team as per standard practice. There is no requirement for participants to attend POAC prior to PIPAC 2 or 3.

6 Bloods prior to PIPAC 1 do not need to be repeated within 7 days of the PIPAC treatment provided they were done at screening/POAC as these patients will not be having systemic chemotherapy. A blood sample should be taken within 7 days prior to PIPAC 2 and 3.

7 ECG required only if indicated by pre-op assessments.

8 CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform. CT scans should be performed at screening, 10-12 weeks and 18-20 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment will be made.

9 QoL questionnaires to be completed alongside CT scans, at baseline, 8-10 weeks post randomisation, 19-21 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.

10 No SACT is to be given in the ovarian group intervention arm. The exception to this rule is for participants who show extraperitoneal disease progression and have not yet completed 3 PIPAC procedures who may have SACT added in at the discretion of their treating PI. If SACT is added, it should be completed 7 days prior to the PIPAC procedure.

11 AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of CTCAE grade ≥3 bowel obstruction.

12 Approximately 30 days after each PIPAC, a RN will call the participant, review their medical notes since their last PIPAC and document the appropriate Clavien Dindo classification(s) for this time period and report AEs/SAEs as required.

13 PCI scoring is to be performed by the surgeon during laparoscopic surgery for PIPAC.

Table 23: Stomach group control arm schedule

Activity	Screening	Randomisation	Each treatment cycle	8-10 weeks post rand	19-21 or 20-22 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
Informed consent	X											
Randomisation		X										
Medical history, pt demographics/ethnicity	X											
Height and weight[1]			X									
Vital signs and physical assessment	X		X									
ECOG	X		X									
Blood test - FBC, U+Es, LFTs, bone profile	X		X									
Blood test - magnesium			X									
Blood test - DPYD[2]	X											
MMR/MSI, HER2 and CPS testing on tumour biopsy[2]	X											
Urine pregnancy test - WOCBP	X											
CT scan and upload to CIMAR[3]	X			X	X	X	X	X	X	X	X	X
QoL questionnaire completion[4]		X (baseline)		X	X	X		X		X		
Administer SACT [5]			X									
Record concomitant medications	X		X									
Report AEs / SAE[6]			X	X	X	X	X	X	X	X	X	X
CRF completion	X	X	X	X	X	X	X	X	X	X	X	X

1 Height to be measured prior to cycle 1 only, weight to be measured prior to all treatment cycles.

2 MMR/MSI, HER2 and CPS testing of tumour biopsy and DPYD blood test can take place any time prior to randomisation.

3 CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform. CT scans should be performed at screening, and then around 8-10 weeks and 19-21 / 20-22 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment) will be made.

4 QoL questionnaires to be completed alongside CT scans, at baseline, 8-10 weeks post randomisation, 19-21 / 20-22 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.

5 SACT is to be administered according to the protocol. Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.

6 AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of CTCAE grade ≥3 bowel obstruction.

Table 24: Stomach group intervention arm schedule

Activity	Screening	Randomisation	Each PIPAC treatment cycle			Each non PIPAC treatment cycle	8-10 weeks post rand	19-21 or 20-22 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
			Pre op	PIPAC treatment cycle	30 days post PIPAC										
Informed Consent	X														
Surgeon – participant consulation[1]			X												
RN – participant phone call[2]			X												
Randomisation		X													
Medical history, pt demographics/ethnicity	X														
Height and weight[3]			X			X									
Vital signs and physical assessment	X		X			X									
ECOG	X		X			X									
Blood test - FBC, U+Es, LFTs, bone profile	X		X[6]			X									
Blood test - magnesium			X[6]			X									
Blood test – DPYD[4]	X														
MMR/MSI, HER2 and CPS testing on tumour biopsy[4]	X														
Urine pregnancy test - WOCBP	X		X												
ECG[7]			X												
CT scan and upload to CIMAR[8]	X						X	X	X	X	X	X	X	X	X
QoL questionnaire completion[9]		X (baseline)					X	X	X		X		X		
POAC[5]			X[4]												
PIPAC procedure				X											
Administer SACT[10]				X		X									

Activity	Screening	Randomisation	Each PIPAC treatment cycle			Each non PIPAC treatment cycle	8-10 weeks post rand	19-21 or 20-22 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
			Pre op	PIPAC treatment cycle	30 days post PIPAC										
Record concomitant medications	X		X			X									
Report AEs / SAEs[11]			X	X	X	X			X	X	X	X	X	X	X
Clavien Dindo classification[12]					X										
PCI scoring[13]				X											
CRF completion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Optional consultation (either in person or virtual) between the PIPAC surgeon and the participant can take place between date of randomisation and date of PIPAC 1 to discuss the participant's upcoming PIPAC procedure.

2 PICCOS RN will call participant approximately 24 hours prior to each PIPAC to ensure the participant is ready for their procedure.

3 Height to be measured prior to cycle 1 only, weight to be measured prior to all treatment cycles

4 MMR/MSI, HER2 and CPS testing of tumour biopsy and DPYD blood test can take place any time prior to randomisation.

5 Between the date of randomisation and the date of the first PIPAC all participants must attend and be reviewed in a POAC either at their recruiting site or the corresponding PIPAC/Type B site. Where possible, blood results from screening or from any pre SACT cycle assessments can be used in the POAC and any additional bloods tests will be done at the discretion of the POAC team as per standard practice. There is no requirement for participants to attend POAC prior to PIPAC 2 or 3.

6 Participants who have SACT and PIPAC in their PIPAC treatment cycles will need to have bloods within 72 hours prior to day 1 of each PIPAC treatment cycle. Results of these bloods should be passed onto the surgical team for review who will then advise on the need for any repeat pre-op bloods prior to the PIPAC procedure in that cycle (depending on the day within the cycle that PIPAC has been scheduled). Participants who have PIPAC only in their PIPAC treatment cycles will need to have bloods within 72 hours prior to the PIPAC procedure (if this is not logistically possible a window of up to 120 hours prior to PIPAC is permitted).

7 ECG required only if indicated by pre-op assessments.

8 CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform, CT scans should be performed at screening, 8-10 weeks and 19-21 / 20-22 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment (SACT/PIPAC) will be made.

9 QoL questionnaires to be completed alongside CT scans, at baseline, 8-10 weeks post randomisation, 19-21 / 20-22 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.

10 SACT is to be administered according to the protocol. Note in PIPAC cycles, the only permitted SACT is nivolumab, trastuzumab and pembrolizumab (as applicable). Washout periods included in the protocol should be observed. Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.

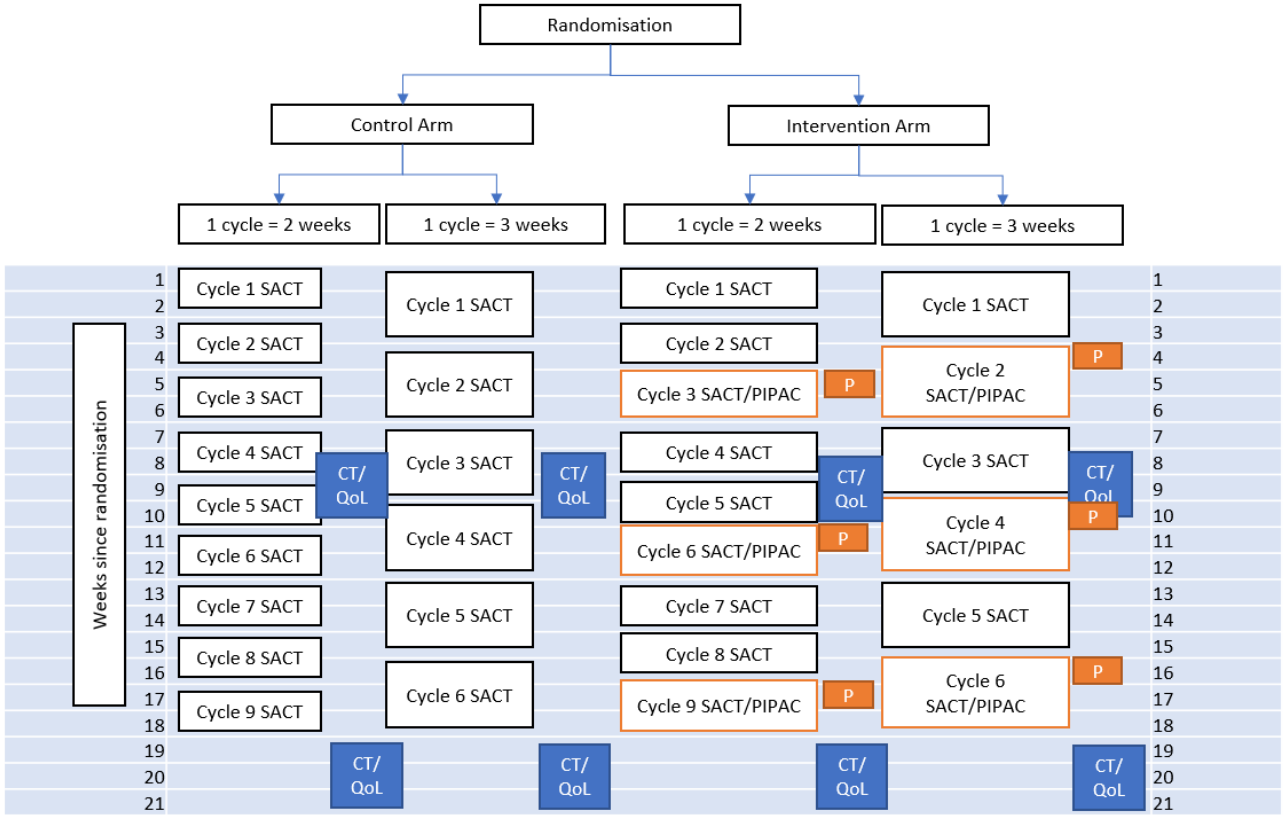
11 AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of CTCAE grade ≥3 bowel obstruction.

12 Approximately 30 days after each PIPAC, a RN will call the participant, review their medical notes since their last PIPAC and document the appropriate Clavien Dindo classification(s) for this time period and report AEs/SAEs as required.

13 PCI scoring is to be performed by the surgeon during laparoscopic surgery for PIPAC.

29.5 PIPAC and SACT schedule vs CT scans and QoL questionnaires

Figure 6: Colorectal group – treatment schedule vs CT scans and QoL questionnaires



CT scans should be scheduled within the blue window shown, if chemotherapy or PIPAC is delayed, the CT scans should go ahead within the original window, but scans should be avoided within 7 days following a PIPAC procedure.

Figure 7: Ovarian group – treatment schedule vs CT scans and QoL questionnaires

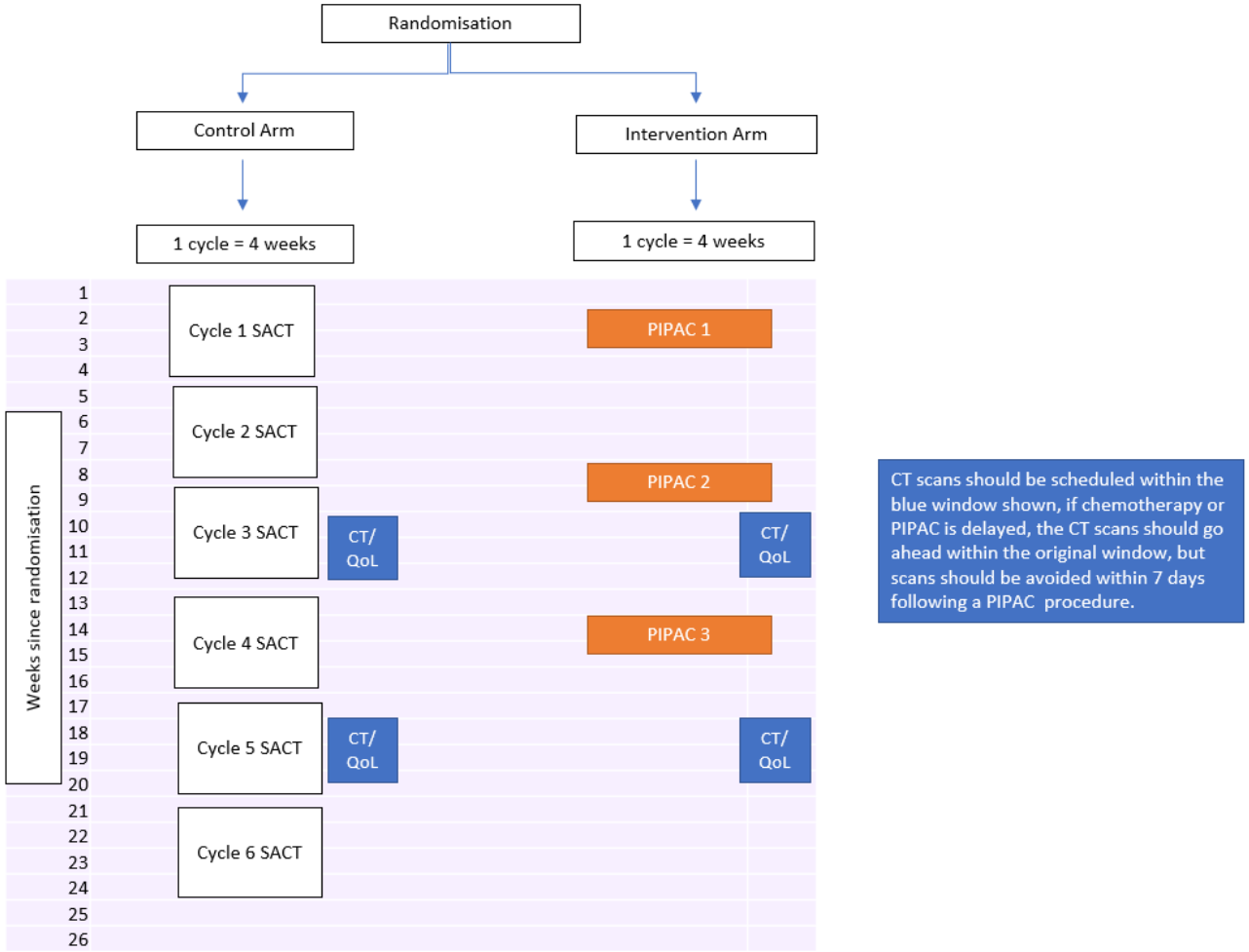
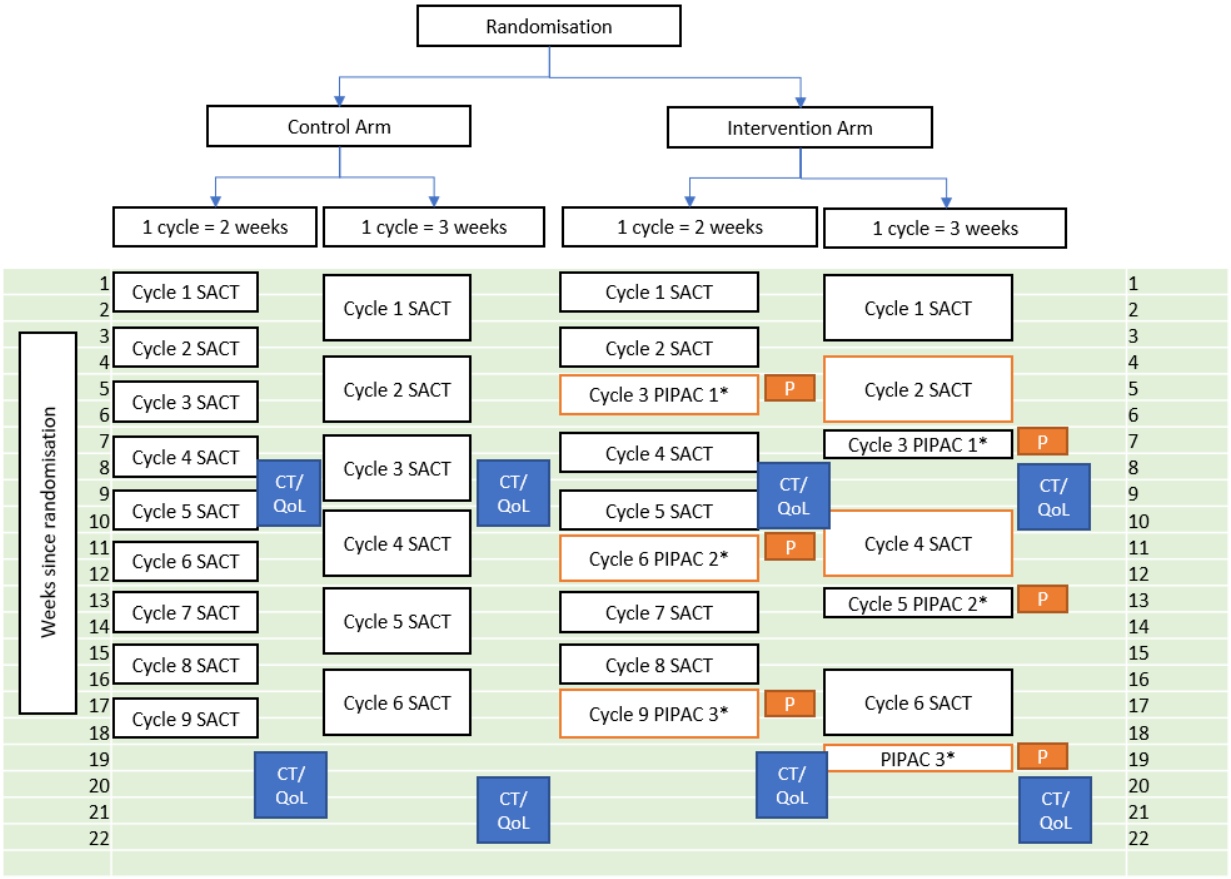


Figure 8: Stomach group – treatment schedule vs CT scans and QoL questionnaires



CT scans should be scheduled within the blue window shown, if chemotherapy or PIPAC is delayed, the CT scans should go ahead within the original window, but scans should be avoided within 7 days following a PIPAC procedure.

29.6 Clavien Dindo classification of surgical complications

Table 25: Clavien Dindo classification of surgical complications (102)

Full Scale			Contracted Form	
Grades	**Definition**		**Grades**	**Definition**
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.		**Grade I:**	Same as for Full Scale
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.			
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.		**Grade II:**	Same as for Full Scale
Grade III:	Requiring surgical, endoscopic or radiological intervention		**Grade III:**	Grades IIIa & IIIb
Grade III-a:	intervention not under general anesthesia			
Grade III-b:	intervention under general anesthesia			
Grade IV:	Life-threatening complication (including CNS complications) ‡ requiring IC/ICU-management		**Grade IV:**	Grades IVa & IVb
Grade IV-a:	single organ dysfunction (including dialysis)			
Grade IV-b:	multi organ dysfunction			
Grade V:	Death of a patient		**Grade V:**	Same as for Full Scale
Suffix 'd':	If the patients suffers from a complication at the time of discharge, the suffix “d” (for ‘disability’) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.			

‡ brain haemorrhage, ischaemic stroke, subarachnoidal bleeding, but excluding transient ischaemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.